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FIELDS OF VISION IN CASES OF TUMOR OF RATHKE'S POUCH

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In 1939 Love, Shelden and Kernohan [1] published a report on 11 consecutive cases of tumor of the hypophysial duct (Rathke's cyst) with particular emphasis on the surgical treatment of this growth. They stated that gradually developing atrophy of the optic nerve was present in 8 cases and papilledema in 3. The defects in the fields of vision were bitemporal in 6 and homonymous in 4. The central vision and fields of vision of a child of 5 years could not be obtained accurately. On reviewing reports of individual cases and analysis of groups of cases, we observed the great variability of the ophthalmologic features of this type of tumor. We were impressed also by the generally pessimistic attitude of neurosurgeons toward the surgical treatment from the standpoint both of operative and of postoperative mortality and of the effect of operation on preservation or improvement of vision. To clarify our own impressions of the results of operations with reference to the eyes, it was thought worth while to analyze somewhat more carefully the preoperative and postoperative ocular findings in the 11 cases already reported and in 12 additional cases in which accurate records of central vision and fields of vision were obtained both before and shortly after surgical removal of the tumor. In this analysis are included also 6 cases in which clinically and at the time of operation the growth was thought to be a cyst of Rathke's pouch, but proved histologically to be an epidermoid tumor. It was thought that a comparison of the ocular findings in the presence of this type of tumor with those associated with the usual craniopharyngioma might be of interest at least to an ophthalmologic group.

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1. Love, J. G.; Shelden, C. H., and Kernohan, J. W.: Tumor of the Hypophysial Duct (Rathke's Cysts): Report of Eleven Consecutive Cases, Arch. Surg. **39**:28-56 (July) 1939.

It is rather difficult to obtain from a survey of the literature any comprehensive impression of the effects of operation on the visual defects caused by craniopharyngiomas. In their book, Bailey, Buchanan and Bucy [2] quoted Cushing: "But all in all these cases offer the most baffling problem which confronts the neurosurgeon. . . . Even from the mere standpoint of preservation of vision the problem is a highly complicated and difficult one." These authors reported 5 cases, all the patients being children. The disks were choked in all the cases. One patient was blind. In 2 cases, the central vision and the fields were normal. In 1 case, the fields were normal but the central vision was reduced preoperatively and returned to normal after operation. In the other case, the central vision was poor and the fields of vision showed generalized and binasal contraction before operation. After operation, the patient was blind. In 1930 Cushing [3] cited 4 cases of craniopharyngioma. Central vision was considerably reduced in all. The defects in the visual fields in 3 were bitemporal and in 1 were associated with central scotomas. In 1 of these cases the disks were normal. In 2, however, it was necessary to section the chiasm in order to expose the tumor; so permanent bitemporal hemianopsia resulted. In the fourth case, both disks were choked, and right homonymous hemianopsia was present. Improvement followed operation but lasted only two months.

In 1927 Peet [4] reported 3 cases of adamantinoma. One of the patients, who had choked disks with secondary optic nerve atrophy, died at operation. The vision of another who had secondary optic nerve atrophy improved slightly in one eye after operation. The third patient, a girl aged 6 years with primary optic nerve atrophy, temporal anopsia in the right eye and amaurosis in the left eye, showed improvement in central vision and in the fields after operation. In 7 of a series of 14 cases reported by Frazier and Alpers,[5] primary optic nerve atrophy was present; the tumor was anterior to the chiasm in 5, posterior to the chiasm in 1 and above the chiasm in 1. In the remaining 7 cases either choking of the disks or secondary optic nerve atrophy was found; the tumor was anterior to the chiasm in 2 and posterior to the chiasm in 5. The fields of vision were recorded in 13 of the cases. They were

2. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Craniopharyngiomas, in Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939, pp. 349-375.

3. Cushing, H.: The Chiasmal Syndrome of Primary Optic Atrophy and Bitemporal Field Defects in Adults with a Normal Sella Turcica, Arch. Ophth. **3**:505-551 (May); 704-735 (June) 1930.

4. Peet, M. M.: Pituitary Adamantinomas, Arch. Surg. **15**:829-854 (Dec.) 1927.

5. Frazier, C. H., and Alpers, B. J.: Adamantinoma of the Craniopharyngeal Duct, Arch. Neurol. & Psychiat. **26**:905-965 (Nov.) 1931.

normal in 2 and generally contracted in 2; the defects were homonymous in 2 and bitemporal in 2. In 4 cases temporal anopsia was present in one eye and amaurosis in the other. One patient was blind. The results of operation from the standpoint of vision were not stated definitely. Frazier and Alpers stated the opinion that tumors arising from the upper anlage of the hypophysial duct may either grow upward and obstruct the third ventricle, with resultant choking of the disks and concentric contraction, or grow downward and result in primary optic nerve atrophy, with bitemporal or homonymous defects in the fields. Tumors arising from the lower anlage should always result in bitemporal hemianopsia, they said.

The series of 7 cases reported by Critchley and Ironside,[6] of 21 cases reported by Beckmann and Kubie and of 4 cases reported by McLean [7] are rather discouraging. Of the cases presented by Critchley and Ironside, choking of the disks or secondary optic nerve atrophy was present in 4 and simple optic nerve atrophy in 3. One patient was blind; the defects in the fields were bitemporal in 4 cases and homonymous in 1. The fields were normal in 1. In 5 cases death occurred in the immediate postoperative period. The fields of vision in 1 case improved immediately after the operation, but the visual defect recurred in two months and the patient died two months after a second operation. In the sixth case, subjective improvement of vision was noted immediately after operation, but three months later the vision had decreased again. The patient died several months after a second operation. Among Beckmann and Kubie's [8] 21 cases, in 3 the fundi were normal, and in 12 they showed optic nerve atrophy and in 6 choking of the disks. These authors were inclined to think that choking of the disks is likely to occur only in children and adolescents. Central vision was reduced in all but 1 of their cases. The fields of vision were normal in 2 cases and showed only generalized contraction in 2. The defects of the fields were homonymous in 3 and bitemporal in 12. In 1 case temporal anopsia was present in one eye and amaurosis in the other. In 1 case vision was reduced to light perception. The mortality in this series was rather high; in 15 of the 21 cases death occurred in the immediate postoperative period. In 6 cases the results of operation could be estimated; vision was worse after operation in 3, was improved temporarily in 2 and remained improved for at least a year in 1. Of the 4 patients reported on by McLean, 3 (1 with secondary optic nerve atrophy, 1 with choked disks and 1 with primary optic nerve atrophy

6. Critchley, M., and Ironside, R. N.: The Pituitary Adamantinomata, Brain **49**:437-481 (Dec.) 1926.

7. McLean, A. J.: Die Craniopharyngealtaschentumoren (Embryologie, Histologie, Diagnose und Therapie), Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:639-682, 1930.

8. Beckmann, J. W., and Kubie, L. S.: A Clinical Study of Twenty-One Cases of Tumour of the Hypophyseal Stalk, Brain **52**:127-170 (July) 1929.

and bitemporal hemianopsia) did not survive operation. Of the other patient, a man aged 27 who had left homonymous hemianopsia, it was stated only that he retained the hemianopsia.

ANALYSIS OF CASES

In our own work, we are accustomed to make a definite ophthalmoscopic diagnosis of simple atrophy of the optic nerve only when definite loss of substance is visible in the nerve head. If only loss of color is observed, the pallor of the disk is graded on the basis of 1 to 4, but the diagnosis of atrophy is not made. Among the 29 cases from the Mayo Clinic included in the present series, the optic disks were normal in 6 and showed pallor alone in 9, simple atrophy in 6 and edema in 8. Loss of vision was a complaint in all but 5 cases. In the remaining 24 there was a history of loss of vision which varied in duration between

TABLE 1.—*Ophthalmoscopic Observations in Cases of Tumor of Rathke's Pouch*

			Epidermoid Tumor		Craniopharyngioma		Duration of Loss of Vision,* Months	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Range	Average
Normal disks	6	21	1	17	5	22	0- 15	7
Choked disks	8	27	..	..	8	35	0- 36	6
Pallor of disks	9	31	5	83	4	17	1- 36	15
Simple atrophy	6	21	..	..	6	26	12-108	38

* By 0 is meant no loss of vision. The average duration of loss of vision is based on all cases in each group whether loss of vision occurred or not.

one and one hundred and eight months. The relationship of the duration of the loss of vision to the appearance of the optic disks is of considerable interest. In cases in which the disks were normal, the duration of the loss of vision varied up to fifteen months and averaged seven months; in cases in which the disks were choked, it varied up to thirty-six months and averaged six months; in cases in which there was pallor of the disks, it varied between one and thirty-six months and averaged fifteen months, and in cases in which there was simple optic nerve atrophy, it varied between twelve and one hundred and eight months and averaged thirty-eight months (table 1).

According to Beckmann and Kubie,[8] choking of the disks may be expected in association with craniopharyngiomas occurring during childhood and adolescence. Our 8 patients with choked disks were 5, 6, 7, 7, 18, 19, 20 and 25 years old, respectively. The location of the tumor as it appeared at the time of operation was stated as intrasellar and suprasellar in 3 cases and posterior to the chiasm in 5. In 1 case in which only pallor of the optic disks was present at the first examination, papilledema developed after operation. The tumor was posterior to,

and above, the chiasm (table 2). In another case the disks were normal at the time of the first examination but choking had developed by the time of the second, approximately six weeks later. This was one of the cases of tumor with suprasellar extension. No choking of the disks was observed in the cases of epidermoid tumor, although in 3 the tumors had suprasellar extension. In all these cases the tumor was anterior to the chiasm (table 2). The patients with epidermoid tumor were 11, 12, 18, 33, 42 and 47 years old. Pallor of the disks

TABLE 2.—*Location of Tumor*

	Epidermoid Tumor	Craniopharyngioma
Anterior to chiasm	6	16
Posterior to chiasm	..	7
Suprasellar extension	3	5*

* Three associated with choked disks.

TABLE 3.—*Field Defects in Cases of Craniopharyngioma and of Epidermoid Tumor*

	Cases	
	Cranio-pharyngioma	Epidermoid Tumor
Bitemporal hemianopsia	2	1
Bitemporal scotoma	1	
Bitemporal hemianopsia with unilateral central scotoma	3	
Bitemporal scotoma with unilateral central scotoma	1	4
Bitemporal hemianopsia with bilateral central scotoma	1	
Temporal anopsia with amaurosis of other eye	2	1
Homonymous hemianopsia	2	
Homonymous hemianopsia with unilateral central scotoma	6	
Generalized contraction	2	
No defects	2	
Fields unobtainable	1	
Total	23	6

without atrophy was present in 5; the disks were normal in 1. In 1, loss of substance occurred after operation.

Of the 5 craniopharyngiomas associated with normal optic disks, 2 were anterior to the chiasm, 1 to the right of the right optic nerve, 1 to the left of the chiasm and left optic nerve and 1 posterior to the chiasm. The 3 remaining tumors which had caused only pallor of the optic disks were all anterior to the chiasm; 1 showed suprasellar extension. All of the 6 craniopharyngiomas which had resulted in simple optic nerve atrophy were anterior to the chiasm; 1 showed suprasellar extension.

Among the cases of craniopharyngioma (table 3), the fields were unobtainable in 1 because of the age of the patient, were normal except

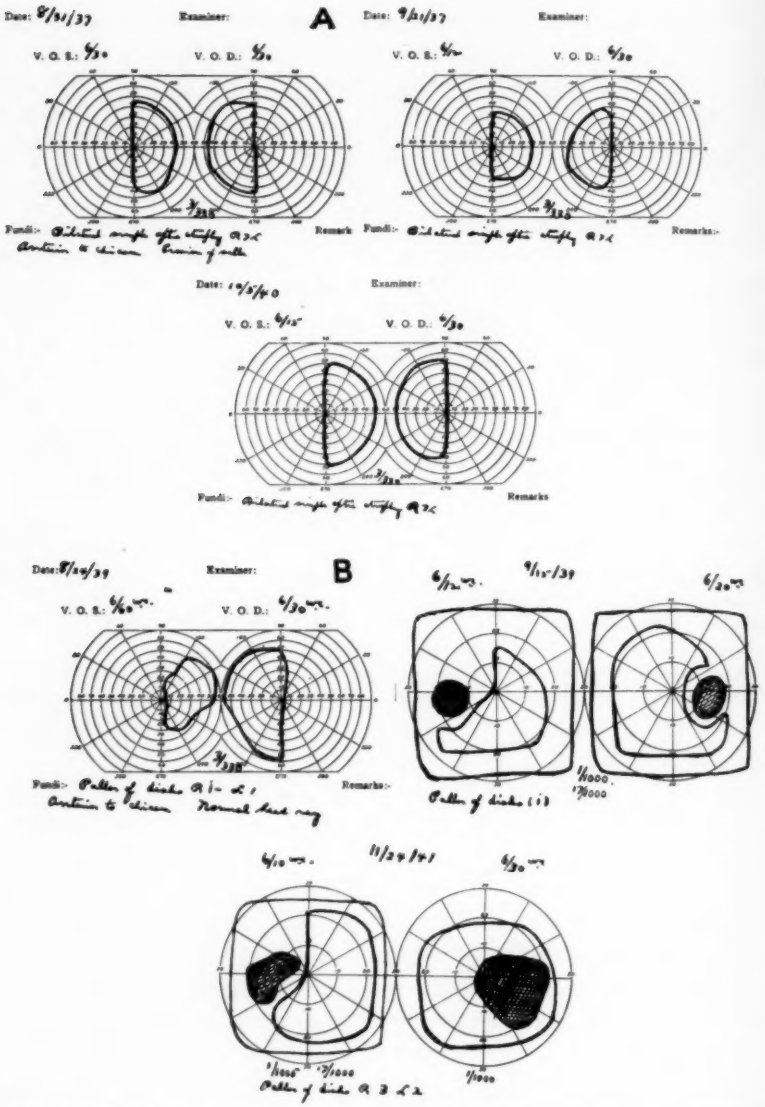

Fig. 1.—Figures 1, 2 and 3 show representative preoperative and postoperative defects of the visual fields associated with craniopharyngiomas and epidermoid tumors.

for enlarged blindspots in 2 and showed concentric contraction in 2, bitemporal defects in 10 and homonymous defects in 8. Among the bitemporal defects, 2 were of the usual bitemporal type, 1 was scotom-

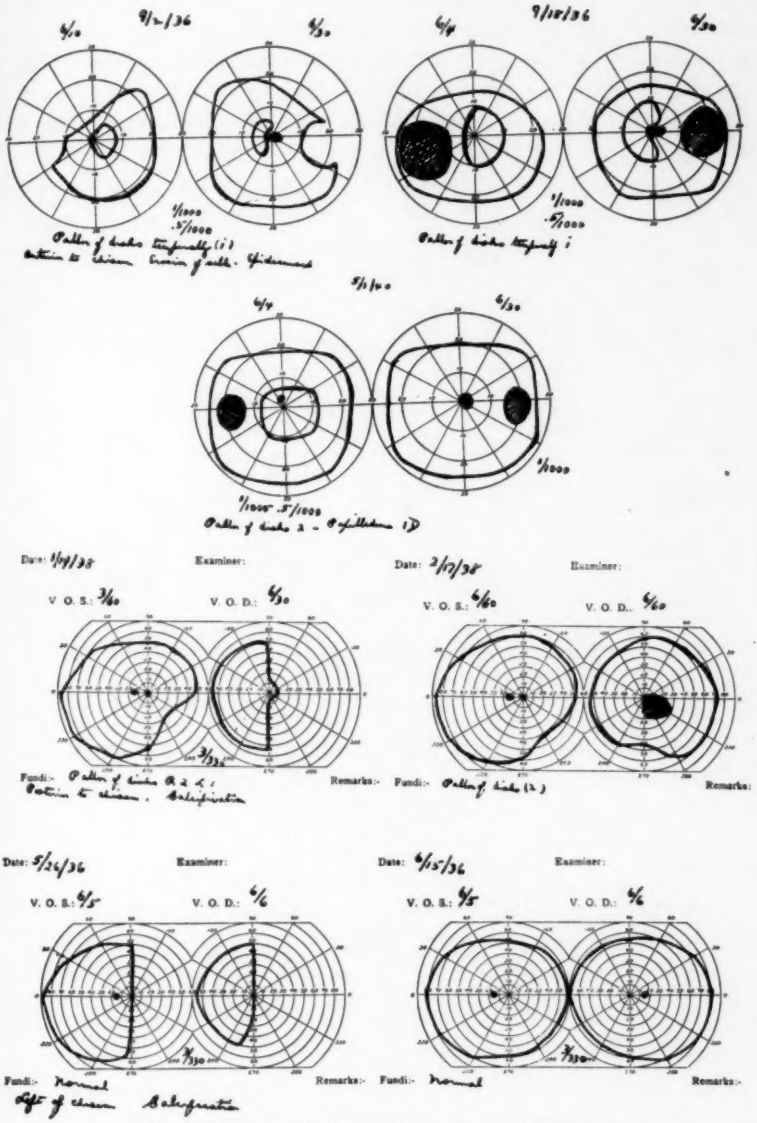

Fig. 2.—Representative defects of the visual fields.

atous, 3 were accompanied with a unilateral central scotoma, 1 was accompanied with bilateral central scotoma, 2 comprised unilateral temporal anopsia with amaurosis in the other eye and 1 was scotomatous

and accompanied with a unilateral central scotoma. Among the homonymous hemiopic defects, 2 were of the usual homonymous type and 6 were associated with a unilateral central scotoma. It is rather striking that in 11 of the 23 cases there were unilateral or bilateral central scotomas and that in 2 others the loss of vision had progressed to complete amaurosis of one eye. In the cases of epidermoid tumor all the

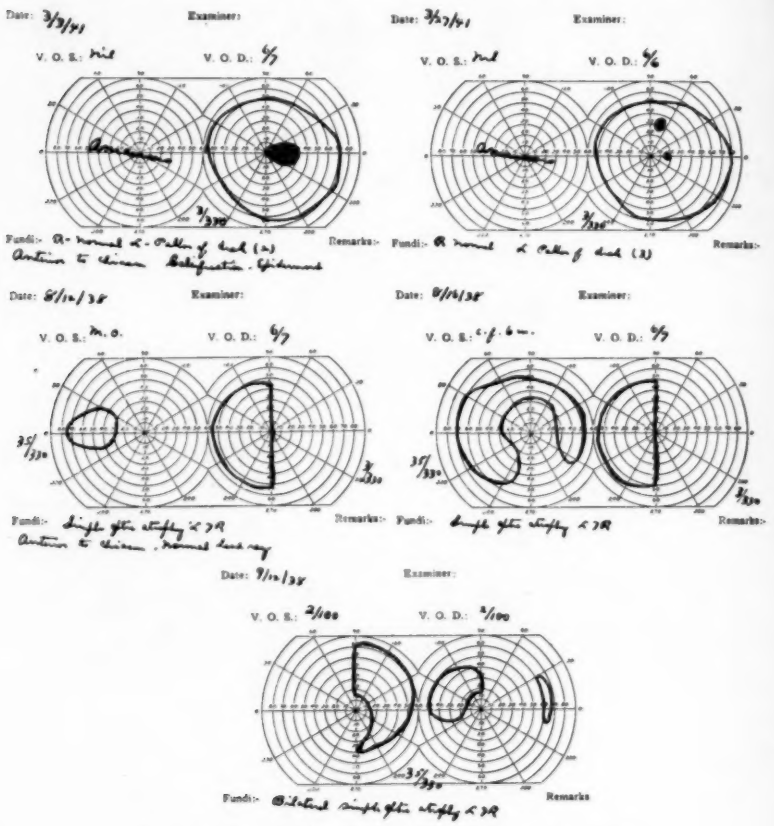

Fig. 3.—Representative defects of the visual fields.

defects were bitemporal; in 4 there was a unilateral central scotoma and in 1 complete amaurosis of one eye (figs. 1, 2 and 3).

In all but 1 of the 16 cases in which the defects were bitemporal, either with or without central scotomas, the tumor was anterior to the chiasm. In this case, in which the defects were bitemporal and scotomatous, the tumor was posterior to the chiasm between the optic tracts. Among the 8 cases in which there was homonymous hemianopsia, the tumor was anterior to the chiasm in 3, posterior to the chiasm in 3, to

the left of the chiasm and left optic nerve in 1 and to the right of the right optic nerve in 1.

In 1 of the cases in which only generalized contraction of the fields was present and in the 1 in which the fields could not be obtained, the tumor was anterior to the chiasm. In the other case in which generalized contraction was present and in the 2 cases in which the fields were normal, the tumor was posterior to the chiasm. In all these cases both disks were choked. Choked disks were observed in 2 of the 8 cases in which the field defects were homonymous and in only 1 of the 16 cases in which they were bitemporal. Peet,[4] however, implied that only generalized contraction of the visual fields will be found in cases of craniopharyngioma with choked disks. Among the 7 cases in this series in which the disks were choked and the fields of vision could be mapped, the fields were normal in 2 and showed generalized contraction in 2, homonymous hemianopsia in 2 and bitemporal hemianopsia in 1.

TABLE 4.—*Primary Presenting Symptoms*

	Epidermoid Tumor (6 Cases)	Craniopharyngioma (23 Cases)
Headaches	3	13
Loss of vision	4	16
Pituitary dysfunction	3	7

Loss of vision was the primary presenting symptom in 16 of the 23 cases of craniopharyngioma and in 4 of the 6 cases of epidermoid tumor (table 4). Loss of vision, however, was noted subjectively in 24 of the 29 cases, including all of the 6 cases of epidermoid tumor. Objectively, central vision was found to be reduced in both eyes in 13 cases and in one eye in 13. Central vision was normal in both eyes in 3 cases of craniopharyngioma.

It is of interest that signs of pituitary dysfunction were presenting symptoms in only 10 of the cases, 7 cases of craniopharyngioma and 3 of epidermoid tumor. It is also noteworthy that diagnostic defects were not present in the roentgenograms of the head in all cases. The roentgenograms of the head, including localized views of the sella and optic foramens, were reported as normal in 7 of the 29 cases. Erosion of the sella was present in 21 cases. Suprasellar or intrasellar calcification was noted in 14.

The ages of the patients varied between 5 and 67 years; 7 patients were in the first decade, 7 in the second, 5 in the third, 5 in the fourth, 2 in the fifth, 2 in the sixth and 1 in the seventh. Thus, 24 of the 29 patients were less than 40. Seventeen of the patients were males, and 12 were females.

RESULTS OF OPERATION

The immediate and late results of operation can be analyzed on the basis of ophthalmoscopic changes, central vision and field defects (tables 5 and 6). In 1 of the 6 cases in which the optic disks had been normal, mild pallor of one disk developed after operation. Of the 8 cases in which both disks were choked, the papilledema decreased in height after operation in 7 and remained the same in 1. Evidence of commencing secondary atrophy of the optic nerve was observed in 4 cases. Of the 9

TABLE 5.—*Immediate Results of Operation: 29 Cases*

	Cases	Condition of Eyes, Cases		
		Improved	Same	Worse
Normal disks	6	..	5	1
Choked disks	8	7	1	..
Pallor of disks	9	..	5	4
Simple atrophy	6	..	6	..
Field changes	28 *	14	6	8
Central vision	28 *	13	7	8

* In 1 case, the central vision and fields were unobtainable because of the age of the patient.

TABLE 6.—*Late Results of Operation: 17 Cases (Four to Eighty-Four Months After Operation)*

	Cases	Condition of Eyes, Cases		
		Improved	Same	Worse
Normal disks	6	..	4	2
Choked disks	2	2 *	..	..
Pallor of disks	2	..	..	2
Simple atrophy	1	..	1	..
Field changes	11	2	2	7
Central vision	11	2	4	5
Report by letter	6	3	2	1

* Moderate secondary optic nerve atrophy developed in both.

cases in which there was pallor of the disks, the pallor was graded the same after operation in 5 and higher in 4. Simple optic nerve atrophy was present in 6 cases before operation and remained unchanged. Among the 28 cases in which central vision and fields of vision could be recorded, the central vision was noted as improved in 13, as unchanged in 7 and as reduced in 8; the fields of vision were noted as improved in 14, as unchanged in 6 and as showing an increase in the defects in 8. In 15 of the 28 cases, some improvement was noted either in the central vision or in the fields of vision, though not necessarily in both central vision and fields in the same patient (fig. 1 *A*).

In 4 of the 8 cases in which there was homonymous hemianopsia, improvement in central vision or fields after operation was noted. In

9 of the 16 cases in which the defects were bitemporal, improvement after operation was noted; in 5 of the 9 cases the tumor was epidermoid. Among the 28 cases in which central vision and fields were obtainable, if we considered each eye separately, there were 14 normal disks, 14 disks with edema, 17 with pallor and 11 with simple atrophy. Improvement in central vision or fields or both was noted after operation in 14 of the eyes with normal disks (100 per cent), in 6 with choked disks (43 per cent), in 7 with pallor (41 per cent) and in 2 with simple atrophy (18 per cent). Central vision and fields remained unchanged in 6 of the eyes with pallor (35 per cent) and in 4 of the eyes with atrophy (36 per cent). Central vision or fields or both were worse after operation in 8 of the eyes with choked disks (57 per cent), in 4 of the eyes with pallor (24 per cent) and in 5 of the eyes with atrophy (45 per cent). Since the development of pallor and simple atrophy in the optic disks seems to be dependent definitely on the length of growth of the tumor, it is obvious that the earlier the diagnosis is established and operation carried out the better will be the results with reference to the preservation and improvement of vision.

Late Results.—From the purely ophthalmologic point of view we are more interested in the late than in the immediate results of operation. It is rather difficult for us to obtain good follow-up studies in cases of the type under discussion. In the main, patients who do well fail to return for observation. Thus we have been able to obtain subsequent data on only 21 of the 29 patients from two and a half to eighty-four months after dismissal from the clinic (table 5). So far as we know, only 4 have died: two and a half months, five months, nine months (after a second operation performed for a recurrence of the growth) and two years, respectively, after the operation. Of the remaining 17, 6 reported by letter only. Of these 6, 3 stated that vision had continued to improve, 2 that vision had remained the same as at the time of dismissal and only 1 that vision had failed further. Of the 11 patients who returned to the clinic for observation, 2 had less marked defects of the fields of vision than at the original dismissal; 2, the same defects, and 7, more marked defects. The central vision of 2 was improved, of 4 was the same and of 5 was worse. It can be said, then, that relatively successful results were obtained from operation in 12 of the 17 cases (71 per cent).

Among the 11 patients who were seen again at the clinic,[9] 6 had normal disks at the time of the first examination (table 6). One of

9. Since this paper was submitted for publication, one of the patients in the series returned for observation, thirty-one months after surgical intervention. At the time of his surgical dismissal, vision was 6/6 + in the right eye and 6/10 + in

(Footnote continued on next page)

these had normal central vision, normal fields and normal fundi four months after removal of the tumor. One patient showed improvement of central vision five months after operation, but a questionable increase in the size of the residual temporal scotoma. Another patient, whose central vision and fields had improved immediately after operation, returned four years later with evidence of hypopituitarism. Central vision and fields, however, were the same as at the time of his dismissal from the clinic, although mild pallor of the optic disks had developed. The 3 other patients who had normal optic disks before operation returned with evidences of recurrence of the tumor three months, six months and one year, respectively, after the original operation. Central vision and fields improved again in 2 of these patients, in 1 after reoperation and in the other after roentgen therapy. Three years after the original operation and two years after the second, the third patient showed some loss of field in one eye but had retained normal central vision and fields in the other eye. Simple optic nerve atrophy was present in one eye and moderate pallor of the disk in the other. Two patients who showed pallor of the optic disks and bitemporal field defects before operation returned two years and three years later, respectively, with central vision and fields better than at the time of their original admission to the clinic and without evidence of recurrence of the tumor, but with a somewhat greater pallor evident in the optic disks. One patient who had bilateral simple optic nerve atrophy at the time of the first admission and whose vision was reduced to a lower nasal field residual in one eye was found to have lost a little more vision one year after operation.

Both of the patients who had choked disks before operation showed bilateral secondary optic nerve atrophy on reexamination one year and four years later, respectively. The first of these patients showed evidence of recurrence of the tumor, and a second operation was performed. Information obtained by letter one year later suggested a further recurrence of the tumor. The second patient did not give any

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the left eye, and the perimetric and tangent screen fields showed relative bitemporal hemianopsia of the scotomatous type. There was bilateral papilledema with elevation of 2 D. in the right eye and 1 D. in the left. On the patient's return to the clinic, the optic disks were normal except for a slight suggestion of pallor, and the vision and fields had remained unchanged. He had definite symptoms and signs of hypopituitarism, with the gonadal features predominating. He was given 25 mg. of testosterone propionate intramuscularly three times a week for four months. At the end of this time, marked improvement in the symptoms of hypopituitarism and a decided improvement in the fields of vision had resulted, so that contraction of the temporal fields was present essentially only for the 1 mm. test object at 1 meter. We have no good explanation for this improvement in the fields of vision.

evidence of recurrence and seven years after operation had retained normal central vision in one eye, with some generalized contraction of the field of vision.

It is evident that simple evacuation of the cystic contents of the tumor will not result in permanent improvement of vision, since if the capsule of the cyst is left behind it is likely to refill and again produce pressure on the optic nerves, chiasm or tracts. The best results will be obtained in those cases in which, because of the small size or favorable location of the growth, extensive resection of the capsule is possible.

SURGICAL PROCEDURES FOR CYSTIC TUMORS ABOUT THE OPTIC CHIASM

If there is evidence of impairment of vision or increased intracranial pressure, then operation for removal of the tumor should not be long delayed. The patient, whether a child or an adult, should have the head completely shaved immediately before going to the operating floor, and a hypodermic injection of atropine sulfate solution, the dose depending on the patient's age and weight, should be given, preferably three quarters of an hour before administration of the anesthetic is started. It seems wiser to shave the head of a child even before the anesthetic is started. In this way an undue prolongation of the anesthesia is avoided and the shaving should not upset the child unduly. The patient is anesthetized first with nitrous oxide and oxygen, and then ether is given until sufficient relaxation is obtained to permit the introduction of the Magill intratracheal tube, over which ether is to be administered by the drop method during the course of the operation. If a very small child takes drop ether well, the intratracheal tube may be omitted in order to prevent edema of the larynx during the postoperative period. However, an intratracheal tube is considered useful, and it gives the anesthetist better control over the patient's respirations during the course of the operation and pure (100 per cent) oxygen can be administered through the tube in order to speed up the patient's recovery from the anesthetic at the completion of the surgical procedure.

The best type of operative procedure to expose the tumor in the region of the chiasm is an extradural approach through a transfrontal bone flap. In this procedure, a curved incision begins at the base of the nose, is passed upward along the sagittal suture and curves laterally and downward in front of the ear. An approach on the right side is preferable, for it is easier to operate through this approach than through a left transfrontal type of exposure. However, if there is a greater loss of vision in the left eye than in the right, indicating greater extension of the tumor to the left than to the right, the approach should be through the left frontal region.

The scalp is turned downward and forward. After a series of five bur holes are made, a bone flap is turned downward toward the temporal region. The dura mater over the frontal lobe is elevated from the roof of the orbit down to the lesser wing of the sphenoid bone. The dura mater then is incised along the wing of the sphenoid, and an intradural approach to the crest of the sella turcica, the tumor and the optic chiasm is employed. The procedure from this point varies somewhat. The variation depends on whether or not the tumor is anterior to the chiasm between the optic nerves, is posterior to the chiasm between the optic tracts or lies laterally between one optic nerve and the internal carotid artery or even underneath the carotid artery. In any event, the cystic tumor should be evacuated, and then as complete a resection as possible of the collapsed capsule should be carried out. When the tumor is posterior to the optic chiasm and the approach to the capsule for its removal is difficult or impossible without sacrifice of some structure, it seems preferable to ligate and divide the anterior communicating artery in order to retract the anterior cerebral arteries laterally rather that to sacrifice the chiasm. The anterior communicating artery has been divided thus with a satisfactory exposure of a tumor which otherwise could not be approached successfully by one of us (Love) in several cases.

It is the practice at the clinic to start a transfusion of blood as soon as the tumor is uncovered and its removal begun. The transfusion is given regardless of whether or not there has been any decrease in the patient's blood pressure. Usually 500 cc. of citrated blood is transfused. Smaller amounts are given to children. After the tumor has been removed and careful hemostasis has been effected, the wound is closed as quickly as possible in order to shorten the time on the operating table. The bone flap is tied in place with two pieces of stainless steel wire, and the pericranium, muscle, temporal fascia and galea aponeurotica are closed in layers with continuous no. 0 chromic catgut. Such closure saves considerable time, and we have not seen any untoward developments from its use. The edges of the skin are approximated with interrupted sutures of silk, or a continuous stitch of silk may be employed in order to conserve time.

During the postoperative period, if hyperpyrexia develops, the patient is placed in an oxygen tent and the temperature within the tent kept at 70 F. The tent is used in preference to the mask, although with the mask a higher concentration of oxygen can be given. The oxygen tent is employed not only for the beneficial effect of the oxygen but in order to place the patient in an artificially cool atmosphere. During the postoperative period, if signs of meningismus develop, lumbar punctures with removal of the hemorrhagic cerebrospinal fluid are carried out daily until the fluid becomes clear. If symptoms of diabetes insipi-

dus develop postoperatively or were present prior to operation, the excessive thirst can be controlled by the insufflation of small amounts of extract of posterior pituitary. Sometimes it is necessary for this substitution therapy to be carried on for a considerable period after the patient returns home. Most often, however, by the time the patient's wound is healed and he is ready to return home, the metabolism of water has become stabilized, and further nasal insufflation is unnecessary.

CONCLUSIONS

1. From the ophthalmoscopic standpoint, a patient with an intrasellar or suprasellar craniopharyngioma or epidermoid tumor may present normal optic disks, choked disks, simple pallor of the disks or simple atrophy of the optic nerve. The two optic disks are not always involved uniformly.

2. Loss of central vision in one or in both eyes is frequent. It was observed in 26 of the 29 cases in this series.

3. The field defects may be either homonymous or bitemporal. Occasionally, only concentric contraction is present, or the fields may be normal.

4. The frequent occurrence of unilateral or bilateral central scotomas or amaurosis of one eye in association with the other defects is striking. This was noted in 64 per cent of the cases in this series. In all but 1 of the cases of epidermoid tumor (83 per cent) this type of defect was present.

5. The absence of sellar erosion or of suprasellar calcification in the roentgenograms of the head cannot be counted on to exclude the presence of tumors of this type. The roentgenograms of the head were normal in 7 of the 29 cases in this series (24 per cent).

6. Early diagnosis and early surgical intervention are essential to the successful treatment of such tumors.

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CHEMOTHERAPY IN OPHTHALMOLOGY

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In the last few years new chemotherapeutic agents have made their appearance. These consist of the well known sulfonamide compounds, already proved valuable clinically, and lesser known substances derived from molds, fungi and bacilli, e. g. penicillin from penicillium, tyrothricin from soil bacteria and actinomycosin from actinomyces. The ophthalmologic literature contains practically no reference to the latter substances. Fleming [1] stated that penicillin is approximately four times as potent as sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), twenty times as potent as sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and one hundred times as potent as sulfanilamide. Penicillin has an important advantage over sulfanilamide in that it is far less toxic and is not inhibited by secretions, pus and large numbers of organisms. Tyrothricin consists of 15 per cent gramicidin and 85 per cent tyrocidin, both of which show marked bactericidal powers for gram-positive organisms. Gramicidin, about twenty-five to fifty times more potent than tyrocidin, is effective in amounts as low as 1 microgram per billion organisms. In the absence of peptones and similar inhibitors, tyrocidin is effective not only against gram-positive but against gram-negative organisms, such as the meningococcus and gonococcus. Penicillin, gramicidin and tyrocidin actually kill organisms, whereas the sulfonamide compounds are merely bacteriostatic. Thus if the former chemotherapeutic agents should prove to be clinically applicable they would be superior in the treatment of infections of the cornea, vitreous and other avascular areas to the sulfonamide compounds, which depend on the mobilization of leukocytes for destruction of the invading organisms.

It is possible that in the future certain ocular infections may be found more responsive to these substances than to the sulfonamide compounds. Further, when an organism has become sulfonamide fast one of these might be substituted. It is likely that the already marked effectiveness of these chemotherapeutic agents may be increased by combining them with other substances, as has been done with the sulfonamide compounds. Branham,[2] working with antimeningococcus serum and these drugs, and other investigators,[3] using antipneumococcus serum, found a combination more effective than either substance alone. Zaytzeff-Jern and Meleney [4] reported that the action of the sulfonamide compounds on staphylococcic infections is enhanced by the addition of bacteriophage, while Thygeson [5] and Allen [6] obtained similar results with these drugs plus staphylococcus toxoid. The following writers found an increased antibacterial effect when other agents were used with the sulfonamide compounds: Osgood and others,[7] adding neoarsphen-

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1. Fleming, A.: Proc. Roy. Soc. Med. **34**:342, 1941.
2. Branham, S. E.: Pub. Health. Rep. **55**:12, 1940.
3. Neter, E.: J. Pharmacol. & Exper. Therap. **74**:52, 1942.
4. Zaytzeff-Jern, H., and Meleney, F. L.: J. Lab. & Clin. Med. **24**:1017, 1939.
5. Thygeson, P.: Treatment of Staphylococcic Blepharitis, Arch. Ophth. **28**:167 (July) 1942.
6. Allen, J. H., in discussion on Thygeson,[5] p. 168.
7. Osgood, E. E.; Brownlee, I. E., and Joski, J.: Am. J. M. Sc. **200**:296, 1940.

amine; Neter,[3] adding azochloramid, and Goldberger,[8] using zinc peroxide, iodine and potassium permanganate.

I[9] was unable to obtain penicillin but tried tyrothricin[10] experimentally and found that when it is placed in the conjunctival sac in 0.5 per cent suspension it is nonirritating but when used in high concentration produces considerable irritation and even cloudiness of the cornea. Clinically, it was applied in several cases of acute conjunctivitis, with unimpressive results. However, further investigation from the ophthalmologic standpoint seems to be warranted. In this report the subject matter is limited to the sulfonamide drugs, and of this group mainly to sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine).

Kolmer and Tuft[11] wrote: "Until the discovery of the effectiveness of the original prontosil [the hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene] in the treatment of streptococcal and staphylococcal infection, the chemotherapy of systemic bacterial diseases was largely disappointing." Likewise, the use of the sulfonamide compounds, passing within a short time from the purely experimental stage to a definite clinical acceptance, has revolutionized the treatment of many ocular infections. The selection of the drug, whenever possible, should be based on a precise knowledge of the bacteria involved and the penetrability of the particular drug into the ocular tissues. These compounds exert their maximum therapeutic effect only with satisfactory concentrations at the site of the infection. For most infections it has been found that concentrations in the blood and tissue between 5 and 10 mg. per hundred cubic centimeters are adequate to insure chemotherapeutic effectiveness; for less susceptible organisms, e. g., the staphylococcus, much higher concentrations of the drugs are required. Large doses for short intervals are preferable to small doses for long periods, for there is evidence that inadequate concentrations of the drugs not only may be ineffective in combating infection but may actually produce a state of hypersensitization, which will preclude their use, or a sulfonamide-fast organism, which will not respond even to larger doses if the need for these should arise.[12] For example, if a simple corneal ulcer treated with subminimal doses developed into a serpent ulcer and then into endophthalmitis, the seemingly logical treatment would be the administration of greatly increased doses, which, however, in the first instance (hypersensitization) would not be tolerated and in the second instance (sulfonamide-fast organism) would be entirely ineffective. It is obviously important, therefore, to acquire a knowledge of the penetration and distribution of the sulfonamide drugs after oral and local administration.

OCULAR PENETRATION OF SULFONAMIDE COMPOUNDS ADMINISTERED ORALLY

Investigation of the four most commonly used sulfonamide compounds—sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine—reveals that sulfanilamide yields the highest concentration in the blood and in the ocular tissues and fluids. Much lower concentrations are reached by the less soluble drugs,

8. Goldberger, H. A.: Am. J. Surg. **56**:353, 1942.
9. Bellows, J.: Unpublished data.
10. The tyrothricin was furnished through the courtesy of Merck & Company, Inc.
11. Kolmer, J. A., and Tuft, L.: Clinical Immunology, Philadelphia, W. B. Saunders Company, 1941,
12. Maclean, I. H.; Rogers, K. B., and Fleming, A.: Lancet **1**:562, 1939. Boak, R. A.; Charles, R. L., and Carpenter, C. M.: Tolerance of the Gonococcus in Vitro for Increasing Concentrations of Sulfanilamide, in Gonococcus and Gonococcal Infection, Publication 11, American Association for the Advancement of Science, 1939, p. 118. Sulphonamide-Resistance, editorial, Lancet **2**:285, 1942.

sulfathiazole and sulfadiazine; whereas the values for sulfapyridine lie between the two extremes.[13] In fact, the concentrations of sulfathiazole and sulfadiazine in the eyeball are, with the exception of those in the cornea and sclera, below the value accepted for chemotherapeutic effectiveness (fig. 1). The consistently high concentrations of the sulfonamide compounds in the cornea noted by Bellows and Chinn and confirmed by Meyer, Block and Chamberlain [14] were explained by the latter investigators as due to a process of adsorption, which in turn might account for the remarkable curative results obtained in trachomatous lesions of the cornea.

Therefore, it may be stated that under ordinary conditions it is only with sulfanilamide or sulfapyridine given orally that one is reasonably certain of providing adequate concentrations in the ocular tissues and fluids. However, it must not be concluded that sulfathiazole and sulfadiazine are contraindicated in the treatment of intraocular infections, for it has been demonstrated that the concentrations of these drugs in the eyeball may be increased by the application of heat or of acetylbetamethylcholine (mecholyl), by paracentesis or by inflammation resulting from infection.[15]

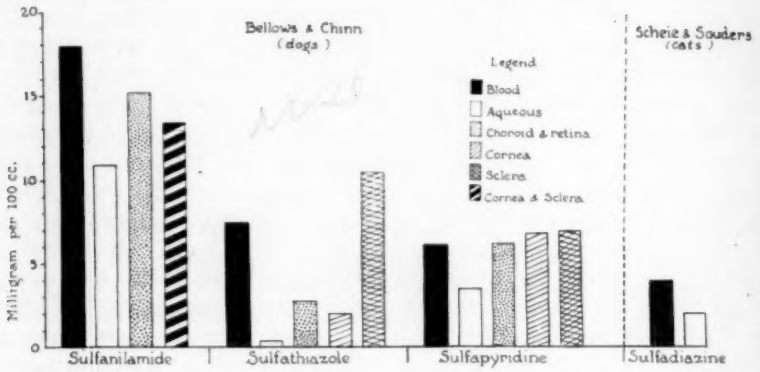

Fig. 1.—Concentration of the sulfonamide compounds in the eye after a single large dose administered orally.

OCULAR PENETRATION OF SULFONAMIDE COMPOUNDS ADMINISTERED LOCALLY

There are two obvious advantages of local application: First, a high concentration is rapidly achieved; secondly, systemic toxic manifestations are avoided. As soon as the therapeutic value of sulfanilamide and its derivatives in ocular infections became evident, investigators [16] sought to determine whether the amount

13. (*a*) Bellows, J., and Chinn, H.: Distribution of Sulfanilamide in Eye, J. A. M. A. **112**:2023 (May 20) 1939; (*b*) Penetration of Sulfathiazole in Eye, Arch. Ophth. **25**:294 (Feb.) 1941. (*c*) Chinn, H., and Bellows, J.: J. Lab. & Clin. Med. **25**:735, 1940; (*d*) Corneal Penetration of Sulfanilamide and Some of Its Derivatives, Arch. Ophth. **27**:34 (Jan.) 1942. (*e*) Scheie, H. G., and Leopold, I. H.: Penetration of Sulfathiazole into Eye, ibid. **27**:997 (May) 1942. (*f*) Scheie, H. G., and Souders, B. F.: Penetration of Sulfanilamide and Its Derivatives into Aqueous Humor of Eye, ibid. **25**:1025 (June) 1941. (*g*) Liebman, S. D., and Newman, E. H.: Distribution of Sulfanilamide and Its Derivatives Between Blood and Aqueous, ibid. **26**:472 (Sept.) 1941.

14. Meyer, K.; Block, H. S., and Chamberlain, W. P., Jr.: Am. J. Ophth. **24**:60, 1941.

15. Bellows and Chinn.[13a] Scheie and Leopold.[13e]

16. (*a*) Lou, T. H., and P'an, S. Y.: Chinese M. J. **58**:167, 1940. (*b*) Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:406 (Sept.) 1939. (*c*) Guyton, J. S.: Am. J. Ophth. **24**:292, 1941. (*d*) Robson, J. M., and Tebrich, W.: Brit. M. J. **1**:687, 1942. (*e*) Bellows and Chinn.[13a] (*f*) Chinn and Bellows.[13d]

reaching the ocular fluids and tissues after topical administration would be equal to that after oral administration. Their results revealed that with a single dose all the drugs with the exception of sulfanilamide reached a higher concentration by oral than by local administration. Owing partly to its greater solubility and small molecular size, sulfanilamide when applied topically reaches a concentration in the eye more than ample for chemotherapeutic effectiveness. The local application of sulfapyridine, sulfathiazole and sulfadiazine produces concentrations in the aqueous humor of less than half the required strength. In penetrability the descending order of the drugs investigated is as follows: sulfanilamide, sulfapyridine, sulfadiazine and sulfathiazole. The penetrability varies not only with the drug used but with the animal, that through the cornea of the rabbit being far greater than that through the cornea of the dog.[18d] Judging from the findings of Lou and P'an, the penetration through the human cornea approaches that through the cornea of the dog (fig. 2).

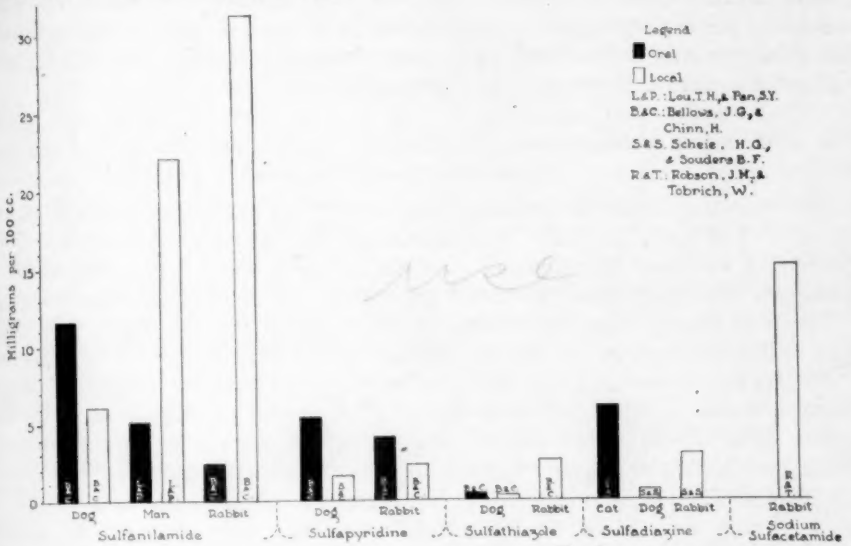

Fig. 2.—Concentration of the sulfonamide compounds in the aqueous humor after a single oral dose or a single local application.

Recently, Boyd,[17] using sulfathiazole, and von Sallmann,[18] using sulfadiazine, demonstrated that a marked increase in the concentrations of these drugs in the cornea and the aqueous humor of the rabbit may be achieved by means of iontophoresis. With a low current no untoward effects were observed. By this method apparently one may attain within the eyeball adequate concentrations of even the sulfonamide compounds with low powers of penetration.

At the present time I have under investigation a simple and yet effective method of increasing the penetrability of sulfanilamide and its derivatives through the use of agents which lower surface tension. Some organic compounds, such as bile salts, sodium laurelate, zephiran (a mixture of high molecular alkyl, dimethyl and benzyl ammonium chlorides) and, among the commercial wetting agents, the aerosols, duponols and ocenols, by reducing the surface tension facilitate penetration through the cornea. For example, the greatest concentration of sulfathiazole within

17. Boyd, J. L.: Sodium Sulfathiazole Iontophoresis, Arch. Ophth. **28**:205 (Aug.) 1942.
18. von Sallmann, L.: Arch. Ophth., to be published.

the aqueous humor after local application is less than 1 mg. per cubic centimeter; with a wetting agent the concentration reaches 10 or even 20 mg. Further studies are under way to determine which of these substances is most practicable for ophthalmologic purposes, since some of them in high concentrations produce cloudiness of the cornea. Although these investigations are still in the incipient stage, it seems likely that there may be at hand a substitute for the oral treatment on which reliance is now placed for the treatment of certain ocular infections.

My investigation of the distribution and penetration of the sulfonamide compounds has led to the following practical conclusions: For intraocular infections sulfanilamide and sulfapyridine given orally, sulfanilamide used topically or any of the four drugs employed with iontophoresis or with a wetting agent will provide an adequate concentration in the ocular tissues and fluids; for conjunctival and corneal disease any of the four drugs in powder or ointment form will give an adequate concentration. At this point it is pertinent to mention a misconception of some authors who report the local use of azosulfamide. Since this drug is reduced to sulfanilamide only within the body,[20] it is obvious that any apparent local effects cannot be ascribed to its sulfanilamide reaction, and its effectiveness is no greater than that of any nonirritating "drops."

OCULAR MANIFESTATIONS OF SYSTEMIC TOXIC REACTIONS TO THE SULFONAMIDE COMPOUNDS

Systemic toxic manifestations are not under consideration, but the report of Martin, Fisher and Thompson [21] is noteworthy in that they demonstrated that the addition of calcium glucuronate, cysteine, ascorbic acid and aminoacetic acid diminishes toxicity without reducing the efficacy of the sulfonamide compounds.

The first report of an ocular manifestation of intoxication due to one of these drugs was given by Bucy,[22] who described a case of optic neuritis which subsided on withdrawal of the drug. A second case was mentioned by Duggan.[23] Baker [24] described a case in which administration of 370 grains (21 Gm.) of sulfanilamide in four days caused round hemorrhages along the course of swollen arterioles. Ocular manifestations vaguely termed "temporary dimness of vision" and "temporary blindness" have been reported in the literature by Colebrook and Purdie [25] and Bloom, Leech and Shaw.[26] Rosenthal [27] observed field changes by means of angioscotometry. Sulfathiazole has been shown by Haviland and Long [28] to produce a conjunctival and scleral injection, restricted to the exposed portions, accompanied by considerable burning and watering. Like other drugs which in large quantities act as poisons, the sulfonamide compounds may produce in the sclera a yellowish discoloration indicating hemolytic or hepatic jaundice and in

19. Footnote deleted.

20. Litchfield, J. T., Jr.; White, H. J., and Marshall, E. K., Jr.: J. Pharmacol. & Exper. Therap. **72**:291, 1941.

21. Martin, G. J.; Fisher, C. V., and Thompson, M. R.: Therapeutic and Prophylactic Detoxication of Sulfanilamide, Sulfapyridine and Sulfathiazole, Arch. Int. Med. **69**:662 (April) 1942.

22. Bucy, P. B.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**: 1007 (Sept. 25) 1937.

23. Duggan, W. F.: Acute Retrobulbar Neuritis as Manifestation of Acute Localized Tissue Anoxia, Arch. Ophth. **25**:299 (Feb.) 1941.

24. Baker, J. P., Jr.: Virginia M. Monthly **67**:562, 1940.

25. Colebrook, L., and Purdie, A. W.: Lancet **2**:1237, 1937.

26. Bloom, W. A.; Leech, M. P., and Shaw, W. J.: J. Missouri M. A. **38**:202, 1941.

27. Rosenthal, C. M.: Changes in Angioscotoma Associated with the Administration of Sulfanilamide, Arch. Ophth. **22**:73 (July) 1939.

28. Haviland, J. W., and Long, P. H.: Bull. Johns Hopkins Hosp. **66**:313, 1940.

the conjunctiva a bluish tinge or pallor suggesting cyanosis or anemia. Transient myopia [29] is by far the most frequent ocular disturbance described. A return to the normal refractive state rapidly follows withdrawal of the drug. In many of the cases, when a cycloplegic was applied the degree of myopia was unaffected, a fact indicating that the changes producing the myopia lie in the crystalline lens rather than in the ciliary body. Bellows and Chinn have demonstrated that sulfanilamide permeates the lens, reaches its peak concentration there and leaves more slowly than it does from other ocular tissues and fluids. This condition is analogous to that found in diabetes mellitus, which results in a "dry salt retention," with its accompanying refractive changes.

LOCAL TOXIC EFFECTS OF SULFONAMIDE DRUGS

While the toxic manifestations following oral administration have been widely reported and are well known, the local toxic effects of the sulfonamide compounds on the ocular tissues have received practically no attention. Bellows and Chinn stated that the local application of sulfanilamide powder to the normal eye for two hours results in a moderate reaction consisting of chemosis and staining of the corneal epithelium. When use of the drug is discontinued the reaction subsides within a short time. Recent work by me [30] indicates that in the absence of normal epithelium the sulfonamide compounds cause a severe injury to the cornea. Thus, if the corneal epithelium of rabbits was removed, the healing time for the untreated eyes averaged five and one-tenth days, while for the treated eyes the average was thirteen and three-tenths days. The time of regeneration in the latter group would have been greater had it not been that in some instances the application of the drug was stopped at the time of complete recovery of the control; in other instances the epithelial regeneration of the cornea did not progress beyond a few millimeters in the periphery until administration of the drug was stopped. Sulfonamide compounds not only cause a delay in the healing of corneal epithelium but cause scars which are highly vascularized. Therefore, after a laceration or abrasion when a minimal amount of scarring is desirable, as on the face or cornea, the local use of a sulfonamide compound should be limited to cases in which dangers of infection outweigh the cosmetic factor.

INDICATIONS FOR ORAL AND LOCAL ADMINISTRATION

Because of the toxicity of these drugs, oral administration should not be utilized indiscriminately or for every slight infection, particularly those infections which are self limited or easily controlled, but should be reserved for serious conditions.

When infection has begun in the interior of the eyeball or has progressed beyond the reach of topical application, oral administration seems to be indicated. The apparent corollary would be that local application is indicated for superficial infections. This, however, is not entirely true. For example, in conditions such as trachoma or gonorrheal conjunctivitis, in which local therapy might be expected to yield most effective results, clinical experience proves oral therapy to be the

29. Landsberg, M.: Visual Disturbance and Sulfanilamide, J. A. M. A. **113**:2260 (Dec. 16) 1939. Mattson, R.: Acta ophth. **17**:314, 1939. Berns, W., cited by Mattson. Spellberg, M. A.: Illinois M. J. **75**:366, 1939. LaGrange, H., and Landot, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **55**:883, 1939. Gailey, W. W.: Am. J. Ophth. **22**:1399, 1939. Bristow, J. H.: Temporary Myopia Due to Sulfanilamide, Arch. Ophth. **24**:799 (Oct.) 1940. Rittenhouse, E. A.: Myopia After Use of Sulfanilamide, ibid. **24**:1139 (Dec.) 1940. Missoroli, A.: Boll. d'ocul. **18**:59, 1940. Hornbogen, D. P.: Am. J. Ophth. **24**:323, 1941. Friedman, B. B.: ibid. **24**:935, 1941. Blankstein, S. S.: ibid. **24**:895, 1941.

30. Bellows, J., and Gluckman, R.: Arch. Ophth., to be published.

superior method. Finally, it must be remembered that a combination of both oral and local administration may in some instances be the best form of therapy.

The effectiveness of local application of sulfonamide compounds to the eye is governed by certain local conditions. Since the cornea is avascular and since the drugs are bacteriostatic rather than bactericidal, the effect is less marked in this tissue than in a vascularized tissue or in the blood stream, with its full complement of bacteria-destroying leukocytes. Further, the effectiveness in this region is decreased by the secretion and detritus so often associated with ocular disease and the frequent use of local anesthetics, such as procaine hydrochloride and related substances, whose structural formulas resemble that of paraaminobenzoic acid. The presence of secretion itself in gonorrheal and trachomatous infections, and all these influences in infectious corneal ulcers, may account for some of the failures in ocular therapy. Although present knowledge is inadequate to provide absolute indications for local and oral administration of sulfonamide compounds in the treatment of many ocular infections, a working plan is essential. In the following sections, recommendations of the majority of ophthalmologists for the treatment of ocular infections are presented.

ERYSIPELAS

Erysipelas, although not primarily an ocular condition, is of interest to the ophthalmologist because of the site of predilection—the inner canthus of the eye—a factor leading to ocular complications: lid abscess, corneal ulceration and orbital cellulitis. The disease is caused by the hemolytic streptococcus. Among the first to use sulfonamide compounds in the therapy of erysipelas were Meyer-Heine and Huguanin.[31] These authors reported that in 150 cases in which a sulfonamide preparation was used orally, the fever and the lesion subsided within forty-eight hours. Similar excellent results have been reported by British and American writers, who stressed a marked decrease in mortality.[32] The keynote of success in the treatment of erysipelas is early administration, as shown by Rantz and Keefer,[33] who stated that it is impossible to demonstrate any effect of the drugs on the course of the disease if administration is begun after the third day. Shank and others[34] stated that "the prompt response of erysipelas to sulfonamides makes this the treatment of choice and renders other therapeutic measures obsolete."

PYOGENIC INFECTION OF THE SKIN OF THE EYELIDS

Impetigo contagiosa is the most common of all the pyogenic infections of the skin and at times involves the skin of the eyelids. It may be of streptococcic, staphylococcic or mixed bacterial origin.[35] It responds to the use of a 10 per cent sulfanil-

31. Meyer-Heine, A., and Huguanin, P.: Presse méd. **44**:454, 1936.

32. Breen, G. E., and Taylor, I.: Lancet **1**:1334, 1937. Snodgrass, W. R., and Anderson, T.: Brit. M. J. **2**:1156, 1937. Hageman, P. O., and Blake, F. G.: Am. J. M. Sc. **195**:163, 1938. Nelson, J.; Rinzler, H., and Kelsey, M. P.: Sulfanilamide Treatment of Erysipelas, J. A. M. A. **112**:1044 (March 18) 1939. Hoyne, A. L.; Wolff, A. A., and Prim, L.: Fatality Rates in Treatment of Nine Hundred and Ninety-Eight Erysipelas Patients, ibid. **113**:2279 (Dec. 23) 1939.

33. Rantz, L. A., and Keefer, C. S.: New England J. Med. **221**:809, 1939.

34. Shank, R. E.; Maxwell, R. W., and Bozalis, G. S.: Sulfonamides in Treatment of Erysipelas, J. A. M. A. **117**:2238 (Dec. 27) 1941.

35. Dohi, K., and Dohi, S.: Arch. f. Dermat. u. Syph. **111**:629, 1912. Lewandowsky, F.: ibid. **94**:163, 1909. Tachau, P., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1934, vol. 9, p. 34. Epstein, S.: Staphylococcic Impetigo Contagiosa, Arch. Dermat. & Syph. **42**:840 (Nov.) 1940. Cruickshank, R.: Lancet **2**:275, 1941.

amide ointment within four to seven days according to Combes and Canizares.[36] However, Schlesinger and Martin[37] stated the belief that a combination of oral and local administration of a sulfonamide compound is superior to either one alone. Likewise, in the treatment of furuncles and eczematoid lesions from which large numbers of staphylococci can be recovered, sulfonamide compounds are of value. In addition, it has been shown that other dermatologic diseases caused by pyogenic organisms, such as superficial ecthyma or secondary infections of dermatosis, clear more rapidly with use of these drugs than with any other form of treatment.[38]

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a contagious virus disease sometimes involving the eyelids, conjunctiva and cornea. Sommerville[39] reported clinical cures in 6 of 8 cases in which sulfapyridine was used. In the other 2 cases administration of the drug was discontinued because of toxic manifestations. Hill and Downing[40] confirmed this observation and reported a cure in an adult who took one tablet of sulfapyridine four times daily for one week (total amount, 12.5 Gm.). If these observations are substantiated, there will be five virus diseases known definitely to respond to sulfonamide compounds: trachoma, inclusion blenorrhea, lymphogranuloma venereum, psittacosis and molluscum contagiosum.

GONORRHEAL OPHTHALMIA

Since the introduction of Crede's method of prophylaxis more than half a century ago, there has been no greater addition to the therapeutic armamentarium for combating gonorrheal ophthalmia than the sulfonamide compounds. The majority of ophthalmologists are agreed that uniformly good results are obtained in the treatment of gonorrheal conjunctivitis with these drugs in that the period of morbidity, that of hospitalization and the incidence of corneal complications are greatly decreased. Gifford[41] wrote that sulfonamide compounds "in sufficient dosage will, in most cases of gonorrheal conjunctivitis, free the secretion of gonococci more quickly than the use of irrigations and foreign protein alone."

The initial reports of pioneers Hageman,[42] Levy,[43] Fernandez and Fernandez[44] and Willis[45] showed the therapeutic value of sulfanilamide. Barbour and Towsley[46] reviewed the reports in the literature and the results in their own cases and concluded that the drug reduces the duration of the disease from weeks to days. In 15 of their cases, smears became negative in an average of four and eight-tenths days. The report of Bower and Frank[47] soon followed. These authors secured

36. Combes, F. C., and Canizares, O.: Sulfanilamide and Allied Compounds, Arch. Dermat. & Syph. **44**:236 (Aug.) 1941.

37. Schlesinger, B. E., and Martin, N. H.: Lancet **1**:527, 1942.

38. Glicklich, E. A.: New England J. Med. **228**:981, 1942. Pillsbury, D. M.; Wammock, V. S., and Livingood, C. S.: Am. J. M. Sc. **202**:808, 1941

39. Sommerville, J.: Brit. J. Dermat. **53**:255, 1941.

40. Hill, W. R., and Downing, J. G.: Molluscum Contagiosum Cured with Sulfapyridine, Arch. Dermat. & Syph. **46**:139 (July) 1942.

41. Gifford, S. R.: A Hand-Book of Ocular Therapeutics, Philadelphia, Lea & Febiger, 1942.

42. Hageman, P. O.: J. Pediat. **11**:195, 1937.

43. Levy, G. J.: Memphis M. J. **12**:192, 1937.

44. Fernandez, L. H., and Fernandez, R. F.: Am. J. Ophth. **21**:763, 1938.

45. Willis, T.: Yale J. Biol. & Med. **10**:275, 1938.

46. Barbour, F. A., and Towsley, H. A.: Experience with Sulfanilamide in Treatment of Gonorrheal Ophthalmia, Arch. Ophth. **22**:581 (Oct.) 1939.

47. Bower, A. G., and Frank, W.: Am. J. Ophth. **22**:833, 1939.

even more striking results in 15 cases, in that the average number of days necessary to obtain negative smears was reduced to two. Sweet [48] demonstrated, in a review of 100 cases of treatment with sulfanilamide and 78 cases of treatment with sulfapyridine gathered from the literature and his own observation, that there were only 4 instances of corneal complications among the former and none among the latter group.

More recent writers have stated that sulfapyridine and sulfathiazole are superior to sulfanilamide in combating gonococcic infection. The wide acceptance and use of sulfapyridine on the continent and by several American investigators attest its efficacy. Most American investigators,[49] however, agree that sulfathiazole surpasses even sulfapyridine as an antigonococcic preparation. Its superiority was demonstrated experimentally by Lawrence, who found that sulfathiazole had greater bacteriostatic power than either sulfanilamide or sulfapyridine. Clinical confirmation was offered by Wong, who observed that negative smears are obtained with sulfathiazole in one day, as compared with the two days required for sulfapyridine. As can be seen from the accompanying table, presenting 253 cases collected from the literature, the average number of days required to obtain negative smears with the use of sulfanilamide was five and eight-tenths in 150 cases; with sulfapyridine, two and six-tenths in 85 cases, and with sulfathiazole, two and three-tenths in 18 cases. The dose must be adequate from the beginning of treatment, or a refractory condition may arise. Such refractoriness as has been shown for the pneumococcus may be due to an acquired tolerance, which may be developed in vitro by a low concentration of the drug and in vivo by administration of inadequate doses. The need for intensive treatment was emphasized by Thayer Willis,[45] Guyton,[16c] Jasseron and Morard [50] and others. Barbour and Towsley [46] pointed out that newborn infants tolerate sulfonamide compounds well and require larger quantities in proportion to weight than adults to obtain a concentration in the blood of the desired level. A concentration of the sulfonamide compound in the blood of 5 to 10 mg. per hundred cubic centimeters should be maintained, and administration of the drug should be continued for several days after three consecutive daily smears have been negative, in order to forestall recurrences.

TABLE 1.—*The Effect of the Sulfonamide Compounds in Gonorrheal Ophthalmia*

Drug	Number of Cases	Average Number of Days Required for Negative Smears
Sulfanilamide *	150	5.2
Sulfapyridine †	85	2.6
Sulfathiazole ‡	18	2.3

* Hageman.[42] Fernandez and Fernandez.[44] Willis.[45] Barbour and Rowsley.[46] Lewis.[49a] Wong.[49b]
† Sweet.[48] Michie, A. M., and Webster, M. H.: Lancet **2**:373, 1938. Sioboziano, H., and Herscovici, P.: Ann. d'ocul. **176**:466, 1939. Sysl, R.: Acta ophth. **17**:466, 1939. Szinegh, B.: Ophthalmologica **99**: 29, 1940. Suarez Gabard, S.: Arch. de oftal. de Buenos Aires **14**:1937, 1939, abstracted, Am. J. Ophth. **24**: 455, 1941. Lewis.[49a]
‡ Lewis.[49a] Wong.[49b]

48. Sweet, L. K.: J. Pediat. **19**:60, 1941.

49. (*a*) Lewis, P. M.: Gonococcic Conjunctivitis, J. A. M. A. **117**:250 (July 26) 1941. (*b*) Mitchell, D.; Greig, C. H., and Uren, J. L.: Canad. M. A. J. **42**:533, 1940. (*c*) Culp, O. S.: J. Urol. **44**:367, 1940. (*d*) Cook, E. N.: Chemotherapy in Urology, J. A. M. A. **115**:2079 (Dec. 14) 1940. (*e*) Gifford, S. R.: Personal communications to the author. (*f*) Guyton, J. S., and Woods, A. C.: Am. J. Ophth. **24**:428, 1941. (*g*) Lawrence, C. A.: Proc. Soc. Exper. Biol. & Med. **43**:92, 1940. (*h*) Wong, R. T.: Chemotherapy in Treatment of Gonorrheal Ophthalmia, Arch. Ophth. **27**:670 (April) 1942.

50. Jasseron, F., and Morard, G.: Arch. d'opht. **3**:875, 1940.

The great majority of writers recommend oral administration, and rightly so, for, as previously mentioned, in the presence of purulent secretion, topical application would be ineffective. Nevertheless, there are American and foreign reports that local application is also effective. Using 0.5 per cent solution of sulfanilamide, Reins and Tibbetts [51] found that in 15 cases of gonorrheal conjunctivitis smears became negative in an average of six and eight-tenths days. However, the concomitant oral administration of the drug in some of their cases because of the presence of the disease in other parts of the body lessens the value of their claims for the efficacy of local application. Panneton [52] achieved excellent results in several cases with topical application of sulfanilamide, but in his cases also the value of the findings is questionable, since smears were not taken at any time. Bruens [53] and Pillat [54] stated that negative smears were obtained, one within twenty-four hours after repeated application of 10 to 30 per cent preparation of N^1—acetylsulfanilamide. Thus far, therefore, no convincing proof has been offered for discarding the oral and adopting the local use of sulfonamide compounds in the treatment of this disease.

TRACHOMA

As a general rule virus diseases are not influenced by sulfonamide compounds, yet there are several notable exceptions mentioned in the literature, such as trachoma, inclusion blenorrhea, lymphogranuloma venereum and psittacosis. The viruses of these four diseases differ from the typical viruses, according to Thygeson,[55] in that the inclusion bodies vary in size, are basophilic rather than acidophilic and stain readily with Giemsa preparation. Both experimental and clinical investigators disagree concerning the effects of sulfonamide compounds in trachoma. Julianelle, Lane and Whitted [56] and Burnet, Cuenod, Nataf and Rousell [57] demonstrated the disappearance of inclusion bodies in sulfanilamide-treated patients. Richards, Forster and Thygeson [58] found that pooled epithelial scrapings from sulfanilamide-treated patients failed to infect baboons. In contrast, Julianelle and Smith [59] stated that the original capacity to infect is not altered by sulfanilamide in vitro.

Regarding their opinions as to the value of sulfanilamide in the treatment of trachoma, most clinicians may be classified into three groups: (1) those who believe that sulfonamide compounds are curative or at least of great value, including Heinemann,[60] Loe,[61] Gradle,[62] Thygeson [63] and Guyton and Woods; [49f] (2) those who classify these drugs as useful adjuncts, including Dik,[64] Lian,[65]

51. Reins, W. J., and Tibbetts, D. B.: Am. J. Ophth. **22**:1126, 1939.
52. Panneton, P.: Am. J. Ophth. **24**:314, 1941.
53. Bruens, E.: Klin. Monatsbl. f. Augenh. **105**:430, 1940.
54. Pillat, A.: Wien. klin. Wchnschr. **53**:806, 1940.
55. (*a*) Thygeson, P.: Treatment of Inclusion Conjunctivitis with Sulfanilamide, Arch. Ophth. **25**:217 (Feb.) 1941. (*b*) Thygeson, P., and Stone, W., Jr.: Treatment of Inclusion Conjunctivitis with Sulfathiazole Ointment, J. A. M. A. **119**:407 (May 30) 1942.
56. Julianelle, L. A.; Lane, J. F., and Whitted, W. P.: Am. J. Ophth. **22**:1244, 1939.
57. Burnet, E.; Cuenod, E.; Nataf, R., and Rousell, L.: Arch. Inst. Pasteur de Tunis **29**:66, 1940.
58. Richards, P.; Forster, W. G., and Thygeson, P.: Treatment of Trachoma with Sulfanilamide, Arch. Ophth. **21**:577 (April) 1939.
59. Julianelle, L. A., and Smith, J. E.: Am. J. Ophth. **25**:317, 1942.
60. Heinemann, H.: Geneesk. tijdschr. v. Nederl.-Indië **77**:1966, 1937.
61. Loe, F.: Sulfanilamide Treatment of Trachoma, J. A. M. A. **111**:1371 (Oct. 8) 1938.
62. Gradle, H., in discussion on Loe.[61]
63. Thygeson, P.: Am. J. Ophth. **23**:271, 1940.
64. Dik, J. H. R.: Geneesk. tijdschr. v. Nederl.-Indië **78**:1614, 1938.
65. Lian, S. B.: Geneesk. tijdschr. v. Nederl.-Indië **78**:1058, 1938.

Schwarz,[66] Szinegh,[67] Gifford,[41] Poleff,[68] Schmid and Saubermann,[69] and Sory,[70] and (3) those who consider them ineffectvie, including Wilson,[71] Busacca[72] and MacCallan.[73]

While evidence is lacking that sulfonamide compounds actually cure trachoma, most clinicians agree that there is improvement in subjective and to a lesser degree in objective symptoms. If improvement rather than cure is taken as the criterion of therapeutic effectiveness, the majority of writers are in essential agreement. Gifford[41] wrote, "There seems to be no doubt that sulfanilamide is useful in trachoma, especially when corneal ulceration and acute inflammatory symptoms are present." There are many cases, however (29 of 77 observed by Smith, Julianelle and Whitted, for example), in which the disease is resistant to therapy with sulfanilamide or a derivative. How the improvement is effected is not clear. One group asserts that the beneficial results obtained in the treatment of trachoma are procured by elimination of the secondary infection. Spink[74] suggested that if this was true sulfapyridine would be superior to sulfanilamide, since the organisms most frequently present are the pneumococcus, the staphylococcus, etc. Others maintain that the drug does not act on the superimposed infection, but on the virus itself. Substantiation for the latter theory is offered by Thygeson,[58] who found that sulfanilamide brought about rapid improvement in trachoma, whereas there was little or no effect on the accompanying organisms. It appears to me that since improvement occurs in related virus diseases (inclusion blennorrhea and lymphogranuloma venereum) which rarely are complicated by secondary infections, the evidence is in favor of the belief that sulfanilamide acts directly on the virus. Further, it is more than probable that the drug effects improvement by concurrent action on both the virus and the secondary organisms. McKelvie, Kirk and Holder[75] depicted the clinical sequence following the institution of sulfanilamide therapy: In the first stage the pressing symptoms, such as pain, photophobia and lacrimation, decrease. The second stage (one to four weeks) is characterized objectively by a gradual clearing of the cornea and subjectively by an improvement of the visual acuity. Finally, the exuberant fleshy granulations decrease; follicular hypertrophy and old corneal scars, however, are improved little or not at all. The fact that old corneal scars remain uninfluenced by sulfanilamide emphasizes the urgency for early treatment.[76] One must not mistake the early and rapid improvement for a cure, because too early withdrawal of sulfanilamide may lead to recurrences. This danger is indicated in Cooper's[77] report of 34 cases, in 21, or 62 per cent, of which there was a recurrence in six to thirty months. His experience is not uncommon among clinicians.[78]

66. Schwarz, J.: Geneesk. tijdschr. v. Nederl.-Indië **79**:1971, 1939.
67. Szinegh, B.: Arch. f. Ophth. **141**:109, 1939; Ophthalmologica **98**:321, 1940.
68. Poleff, L.: Presse méd. **48**:235, 1940.
69. Schmid, A. E., and Saubermann, G. B. C.: Ophthalmologica **103**:65, 1942.
70. Sory, R.: Am. J. Ophth. **25**:713, 1942.
71. Wilson, R. P.: Giza Mem. Ophthalmic Lab., Ann. Rep. **13**:103, 1938; abstracted, Am. J. Ophth. **24**:1456, 1941.
72. Busacca, A.: Folia clin. et biol. **12**:63, 1940.
73. MacCallan, A. F.: Brit. M. J. **1**:482, 1940.
74. Spink, W. W.: Sulfanilamide and Related Compounds in General Practice, Chicago, The Year Book Publishers, Inc., 1941.
75. McKelvie, A. R.; Kirk, R., and Holder, H. J.: Am. J. Ophth. **24**:1035, 1941.
76. Lian, S. B.: Ophthalmologica **98**:208, 1939. Richards, Forster and Thygeson.[58]
77. Cooper, W. L.: Management of Recurrent Trachoma Following Sulfanilamide Therapy, Arch. Ophth. **24**:467 (Sept.) 1940.
78. Smith, J. E.; Julianelle, L. A., and Gamet, J. H.: Am. J. Ophth. **24**:174, 1941.

There are a few reports in the literature indicating that topical application [79] and subconjunctival injections [80] may be effective, but oral administration is the generally accepted method. In fact, Thygeson stated that local therapy is entirely ineffective. The most effective results are obtained by intensive treatment for a short time rather than administration of small fractional doses over a protracted period.[81] Smith, Julianelle and Gamet,[78] in a critical review of the literature, found variations in doses from 15 to 90 grains (1 to 6 Gm.) a day and in duration of treatment from a few days to more than seventy days. These factors may account for some of the differences in effectiveness reported.

Although marked improvement may be obtained by the use of sulfanilamide alone, the great majority of writers believe that results are far better when this is supplemented by local therapy with copper or silver salts or grattage.

INCLUSION CONJUNCTIVITIS

Inclusion conjunctivitis, like trachoma, is a virus disease which responds favorably to therapy with the sulfonamide compounds.[82] Thygeson found that the time for healing decreased from three or five months to two weeks in the case of infants and only slightly less in that of adults. Guyton obtained cures in 2 cases within six days. Epithelial scrapings become negative for inclusion bodies in two to four days (Thygeson, Allen), but in some instances inflammatory signs may abate before the disappearance of the inclusion bodies (Schmid and Saubermann). As in trachoma, papillary hypertrophy responds more promptly to therapy than follicular hypertrophy. Unlike trachoma, however, inclusion blenorrhea is rarely complicated by secondary infections, and one may assume with Thygeson that improvement must be the result of the action of sulfanilamide in interrupting the intracellular development of the virus. Thus, it seems that the local application of sulfathiazole is the treatment of choice for inclusion conjunctivitis.

OPHTHALMITIS DUE TO LYMPHOGRANULOMA VENEREUM

Ocular infection with lymphogranuloma venereum is rare, but, whether it is conjunctivitis, keratitis or iritis, a sufficient number of reports exists to indicate that the disease responds to therapy with the sulfonamide compounds as rapidly in the eye as in other parts of the body.[83] Like trachoma and inclusion blenorrhea,

79. Rambo, V. C.: Am. J. Ophth. **21**:739, 1938. Cosgrove, K. W.: ibid. **23**:911, 1940. Lee, O. S.; Rottenstein, H. S., and Chao, H. Y.: Chinese M. J. **60**:207, 1941. Paton, R. T.: Subconjunctival Injections of Neoprontosil in Treatment of Ocular Infections, Arch. Ophth. **22**:377 (Sept.) 1939.

80. Dejean, C., and Roux, J.: Treatment of Trachoma by Certain Sulfamides in Subconjunctival Injections, Bull. Soc. d'opht. de Paris, 1939, p. 202; abstracted, Am. J. Ophth. **24**:720, 1941.

81. Tiscornia, A., and Moret, R. L.: Arch. de oftal. de Buenos Aires **14**:825, 1939; abstracted, Am. J. Ophth **24**:964, 1941. Guyton.[49f] Thygeson.[63]

82. Giddens, S. W., and Howard, W. A.: M. Ann. District of Columbia **9**:333, 1940. Allen, J. H., in discussion on Thygeson.[55a] McCallan, A. F.: Brit. J. Ophth. **26**:271, 1942. Guyton, J. S.: Am. J. Ophth. **22**:839, 1939. Thygeson.[55]

83. Ouwejan, A. J.: Parinaud's Oculoglandular Syndrome and Venereal Lymphogranuloma, Geneesk. tijdschr. v. Nederl.-Indië **79**:1409, 1939; abstracted, J. A. M. A. **113**:1083 (Sept. 9) 1939. Meyer, G. P., and Reber, J.: Am. J. Ophth. **24**:161, 1941. Curth, W.; Curth, H. O., and Sanders, M.: Chronic Conjunctivitis Due to Virus of Venereal Lymphogranuloma, J. A. M. A. **115**:445 (Aug. 10) 1940. Macnie, J. P.: Ocular Lymphogranuloma Venereum, Arch. Ophth. **25**:255 (Feb.) 1941.

it is caused by a virus. Stein [84] advised that ordinary forms be treated with the following doses: 4 Gm. daily for four weeks, 5.3 Gm. daily for three weeks or 6.6 Gm. daily for two weeks.

ACUTE CONJUNCTIVITIS

Although most of the organisms causing acute conjunctivitis are admittedly sensitive to these drugs, the necessity of using the sulfonamide compounds locally in the treatment of acute conjunctivitis is questionable, if one may judge from reports in the literature.

In cases of acute conjunctivitis caused by Koch-Weeks organisms, Wilson observed that the drugs did not shorten the period of morbidity. Thygeson stated that sulfanilamide had no effect on Haemophilus influenzae, Diplococcus pneumoniae and Staphylococcus complicating trachoma. Guyton, in 18 cases of acute bilateral conjunctivitis caused by Koch-Weeks bacillus, the staphylococcus, the streptococcus and the pneumococcus, noted that the infections in the eyes receiving a bland ointment cleared as rapidly as those treated with a sulfanilamide ointment. Schmid and Saubermann agreed that the results of chemotherapy are unimpressive. Guyton and Woods demonstrated that sulfonamide compounds administered orally for severe infections markedly decreased the healing time. However, in the ordinary case acute conjunctivitis is too mild and self limited to require so drastic a measure as oral therapy.

BLEPHARITIS

The most frequent form of blepharitis is caused by the staphylococcus. Treatment has been unsatisfactory until recently. The simple application of sulfathiazole results in a local concentration sufficiently high to combat this stubborn disease without danger of systemic toxicity. According to Thygeson [5] a dramatic response is obtained by using it four to six times daily in a 1 to 5 per cent ointment. Even better results were noted when it was used in conjunction with injections of staphylococcus toxoid. Allen [6] confirmed this observation and stated that of 40 patients treated with the combined method, 34 had negligible symptoms within one to four weeks. Since Zaytzeff-Jern and Meleney [4] reported that sulfonamide compounds with bacteriophage are highly effective against staphylococcic infection, is it not possible that a similar combination might be effective in this disease?

SERPENT ULCER

Since serpent ulcers are caused by the pneumococcus and rarely by other organisms, such as the Morax-Axenfeld hemophilus and Bacillus pyocyaneus, all of which are sensitive to sulfonamide compounds, one is justified in using these drugs. Reports are available showing the value of chemotherapy in this condition. Thus, Bailey and Saskin [85] procured remarkable improvement in 6 cases, Roggenkamper [86] obtained striking results in 15 cases, and de Bascaran [87] reported comparable results in 10 cases of serpent ulcer treated with sulfonamide compounds. However, in the reports of these authors bacteriologic examinations were either few in number or not mentioned. Other clinical observations have been made by Rosengren,[88] Chamberlain,[89] Guyton and others. It has been demonstrated

84. Stein, R. O.: Am. J. Syph., Gonor. & Ven. Dis. **24**:454, 1940.
85. Bailey, J. H., and Saskin, E.: Treatment of Severe Corneal Ulcer with Sulfanilamide, Arch. Ophth. **22**:89 (July) 1939.
86. Roggenkamper, W.: Klin. Monatsbl. f. Augenh. **103**:211, 1939.
87. de Bascaran, A.: Semana méd. españ. **3**:409, 1940; cited by Chamberlain.[89]
88. Rosengren, B.: Acta ophth. **17**:209, 1939.
89. Chamberlain, W. P., Jr.: Treatment of Pneumococcic Corneal Lesions, Arch. Ophth. **27**:869 (May) 1942.

experimentally and clinically that sulfonamide compounds are effective in the treatment of B. pyocyaneus ulcer. Joy [90] and Lepard [91] administered the drugs by the oral route, von Sallmann [18] by iontophoresis and Robson and Scott [92] by drops. Joy concluded his excellent investigation by stating that

> the oral administration of sulfapyridine sodium is effective in the prophylaxis and the treatment of experimental B. pyocaneus ulcer of the rabbits' cornea and . . . the efficacy of the treatment varies directly with the promptness with which it is instituted.

In contrast to these good results, those obtained in the treatment of experimentally produced pneumococcic ulcers were disappointing according to Chamberlain, who found that while sulfapyridine caused an improvement in the conjunctival condition associated with serpent ulcer the effect on the cornea was unimpressive. In 2 cases of pneumococcic serpent ulcer which I observed, the lesions progressed in spite of early chemotherapy with a sulfonamide compound, keratotomy finally being required in each. The explanation for the poor results observed in some cases of serpent ulcer may lie in a delay in application of the drug or in the factors retarding the action of sulfanilamide, the avascularity of the cornea, the use of local anesthetics or the presence of secretion and detritus, as mentioned previously.

CELLULITIS OF LIDS AND ORBIT

Sulfanilamide is effective in the treatment of streptococcic infections of the lids and orbit. Spink [74] stated that to be effective in cellulitis treatment should be instituted early and the concentration in the blood should be high. It must be remembered that pus should be drained when localization occurs, so that the action of the sulfanilamide will not be inhibited. The first cases of orbital cellulitis satisfactorily treated with sulfanilamide were reported by Goldenburg [93] and Szinegh; [94] the latter also obtained good results in lid infections. Guyton observed 5 cases of lid and orbital infections; in 4 beta hemolytic streptococci were observed on culture. The infection began to subside within twenty-four hours after the institution of sulfanilamide therapy. A later report described an additional case in which the outcome was satisfactory. Further substantiation of its effectiveness was offered by Swigert,[95] who reported 2 cases of orbital cellulitis in which rapid improvement followed drainage of purulent material and administration of sulfanilamide.

SYMPATHETIC OPHTHALMIA

Despite its importance, there are relatively few reports of the effects of the sulfonamide compounds on sympathetic ophthalmia. Gamble [96] presented before the Chicago Ophthalmological Society in May 1939 a case in which, while the disease had not been cured, it had been kept under control with sulfanilamide. When an opportunity to examine the eyes histologically was afforded by the accidental death of the child, microscopic studies revealed that in spite of the use of large doses of the drug and the satisfactory clinical appearance, the disease process

90. Joy, H. H.: Treatment of Experimental Bacillus Pyocyaneus Ulcer of Cornea with Sulfapyridine, Arch. Ophth. **27**:1135 (June) 1942.

91. Lepard, C. W.: Bacillus Pyocyaneus Ulcer, Arch. Ophth. **28**:180 (July) 1942.

92. Robson, J. M., and Scott, G. I.: Brit. M. J. **1**:5, 1942.

93. Goldenburg, M.: Am. J. Ophth. **21**:54, 1938.

94. Szinegh, B.: Orvosi hetil **82**:527, 1938; abstracted, Zentralbl. f. d. ges. Ophth. **42**:170, 1938.

95. Swigert, J. L.: Am. J. Ophth. **23**:84, 1940.

96. Gamble, R.: Am. J. Ophth. **24**:49, 1941.

had still been active. Colenbrander [97] reported an astonishing improvement in the sympathizing eye in a proved case of sympathetic ophthalmia treated with sulfapyridine and a liver preparation. Gifford [98] has observed 6 cases of sympathetic ophthalmia, in 4 of which the disease responded unusually well.

TABLE 2.—*Effect of the Sulfonamide Compounds on Panophthalmitis* *

No. of Cases	Organism	Drug	Effect
2	Streptococcus haemolyticus..... Staphylococcus	Sulfanilamide	Subsidence of infection in both eyes
3	.....	Sulfanilamide	Destruction of 2 eyes; healing of 1
2	.....	Sulfapyridine.	Complete healing
2	.....	Sulfathiazole	Complete healing
1	Meningococcus.....	Sulfanilamide	Dramatic cure
1	Bacillus pyocyaneus.....	Sulfanilamide	No effect
1	Bacillus coli and staphylococcus	Sulfamethylthiazole †	Doubtful effect

* Data taken from Guyton and Woods.[49f]
† 2-(paraaminobenzenesulfonamido)-4-methyl-thiazole.

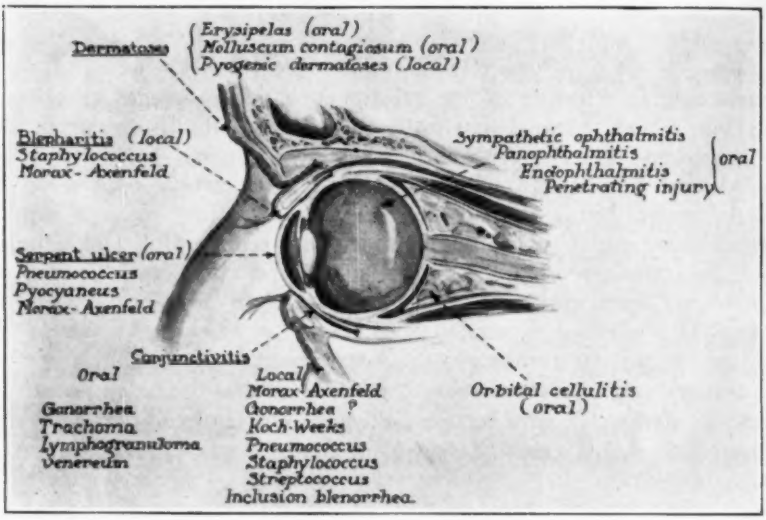

Fig. 3.—Indications for the use of the sulfonamide compounds in the treatment of ocular infections.

ENDOPHTHALMITIS AND PANOPHTHALMITIS

In endophthalmitis and panophthalmitis, as in other diseases in which purulent matter and detritus appear, the sulfonamide compounds to be effective must be used early. However, even in ordinary clinical cases, in which the time of initial treatment frequently cannot be chosen, the results are not entirely discouraging. Thus, in 3 of 7 cases of endophthalmitis and panophthalmitis reported by Guyton the outcome was satisfactory, and of 6 cases of endophthalmitis mentioned by Guyton and Woods, healing was rapid in 3 and was accompanied with organization of the vitreous in 1, and the drugs had no effect in 2. The results in panophthalmitis reported by these authors were even more encouraging, for in 9 of 13 cases

97. Colenbrander, M. C.: Belangreiche Besserung sympathischer Ophthalmie duch Anwendung von Dagnen und Einspritzungen von Leberpräparaten, Geneesk. tijdschr. v. Nederl.-Indië, 1939; abstracted, Zentralbl. f. d. ges. Ophth. **45**:232, 1940.

98. Gifford, S. R.: Personal communication to the author.

(or 69 per cent) complete healing occurred (table 2). It is probable that the percentage of cures would have been even higher had all the staphylococcic infections been treated with sulfathiazole or sulfapyridine rather than with sulfanilamide.

SUMMARY AND CONCLUSION

1. Penicillin, tyrothricin and similar substances obtainable from molds, fungi and bacteria, while not yet employed clinically in ophthalmology, give promise of future usefulness.

2. Sulfanilamide or sulfapyridine given orally, sulfanilamide used topically or any of the four most commonly used sulfonamide compounds employed with iontophoresis or combined with a wetting agent results in a chemotherapeutically adequate concentration in the ocular fluids and tissues.

3. The action of these drugs is known to be inhibited by the secretion and detritus so commonly associated with ocular infection, by local anesthetics and by the factors inherent in the avascularity of the cornea.

4. Oral administration of sulfonamide compounds frequently produces ocular indications of systemic toxicity.

5. Topical application of these drugs to the denuded cornea retards epithelial regeneration and promotes scarring.

6. Given orally they are effective in the treatment of ocular complications of erysipelas, gonorrheal ophthalmia, trachoma, inclusion blenorrhea, ophthalmitis due to lymphogranuloma venereum, serpent ulcer, cellulitis of the lids and orbit, endophthalmitis, panophthalmitis and sympathetic ophthalmia (fig. 3).

7. Applied locally they are effective in pyogenic dermatoses, infectious blepharitis and some forms of acute conjunctivitis.

In conclusion it may be stated that, although the sulfonamide compounds have proved to be the most important addition to the armamentarium of the ophthalmologist since the introduction of organic arsenicals, they should not be used indiscriminately or be considered a panacea.

720 North Michigan Avenue.

MICROPSIA AND TELEOPSIA LIMITED TO THE TEMPORAL FIELDS OF VISION

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Micropsia, teleopsia and metamorphopsia are known to occur with lesions in the brain.[1] These visual disturbances are usually attributed to disease of the cortex of the occipital lobe. However, they may exist in patients with lesions in the optic pathways anterior to the lateral geniculate bodies. Wilbrand and Sänger[2] pointed out that sometimes metamorphopsia and micropsia precede the formation of absolute scotomas in cases of retinal lesions. They considered these conditions as retinal metamorphopsia and micropsia.

Recently we encountered unusual visual symptoms in a patient with a verified tumor of the chiasmal region. The bitemporal field defects were incomplete. There were spotty asymmetric scotomas with islands of micropsia and of teleopsia limited to the temporal halves of the fields of vision.

A. W., a butcher aged 35, entered the hospital Feb. 10, 1942 with chief complaints of headache and blurred vision. In 1940 he had had headaches, diminution in vision, loss of libido, excessive thirst and frequency of urination. With anterior pituitary extract administered over a period of six weeks, his condition improved. The headaches and blurring of vision lessened, and the polydipsia and polyuria disappeared, and recently the libido had returned. He also lost most of his axillary and chin hair, but during the period of improvement some of the hair on his chin began to grow again.

Two months before admission to the hospital, about a day after extraction of a tooth, the patient had severe bifrontal headache, which was aggravated by coughing and straining. During the height of the headaches vision in the lateral fields became blurred. When the headaches receded, the vision improved. There had been a progressive decrease in the general visual acuity. He had gained 10 pounds (4.5 Gm.). The symptoms of polyuria, polydipsia and lack of libido had not returned.

From the Neurologic Service of Dr. I. S. Wechsler, Mount Sinai Hospital.

1. van Bogaert, L.: Sur des changements métriques et formels de l'image visuelle dans les affections cérébrales (Micropsies, macropsies, métamorphopsies, téléopsies), J. belge de neurol. et de psychiat. **34**:717-726 (Dec.) 1934.

2. Wilbrand, H., and Sänger, A.: Die Neurologie des Auges: Ein Handbuch für Nerven- und Augenärtze, Wiesbaden, J. F. Bergmann, 1906, vol. 3, pt. 2, p. 497.

Examination disclosed that the patient was well nourished, with a hypopituitary habitus, scanty beard, scanty axillary and pubic hair, somewhat enlarged breasts, acromegaloid hands and smooth skin. The neurologic examination gave negative results except to reveal the changes in the visual fields. The disks were pale pink. Perimetric and campimetric examinations revealed areas of blurred vision and

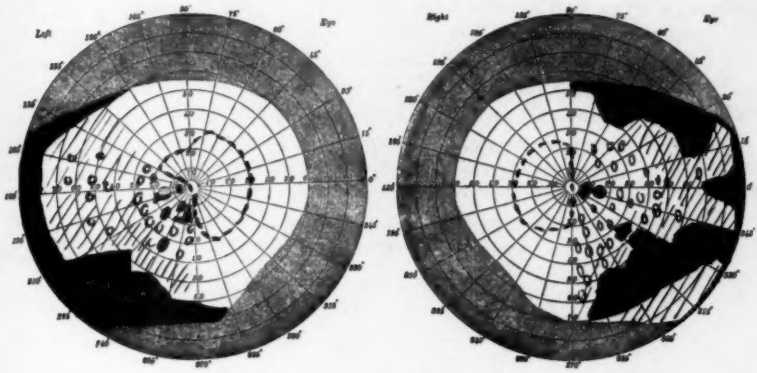

Fig. 1.—The perimetric fields, showing the nature of the bitemporal field defects. The circles indicate islands of micropsia and teleopsia. The areas shaded with diagonal lines represent zones of blurred vision. The solid black areas indicate absolute scotomas. The half-circles in dashes outline the color fields.

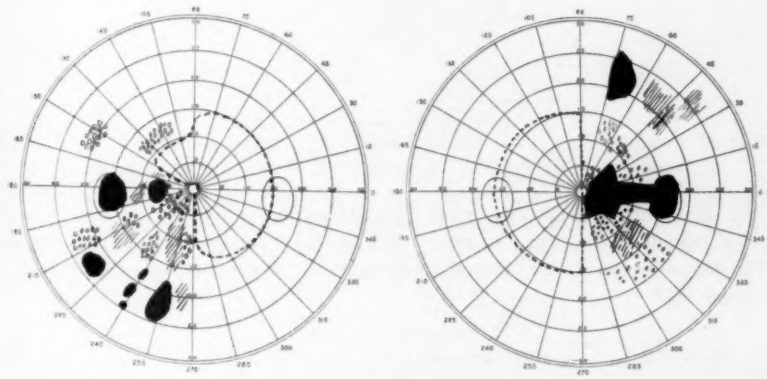

Fig. 2.—The campimetric fields. The markings have the same significance as in figure 1. Note the tendency for the defects to form islands.

multiple small irregular scotomas in the temporal fields, chiefly in the inferior quadrants (figs. 1 and 2). During the examinations the patient stated that he saw the test objects in the temporal fields but that they appeared small and distant, so small, in fact, that he was unable to identify the form of the images. However, when the test object was large enough, he was able to describe it. Thus, while a finger appeared normal when held in the nasal field, it seemed distant and two thirds of its actual size when held in the temporal field.

The micropsia and teleopsia were particularly evident in the lower quadrants of the temporal halves. Whereas the patient was able to reach correctly for a coin in the nasal field, he hesitated and had difficulty in gaging the distance when he attempted to reach for it when it was seen in the temporal field. A 25 cent piece viewed in the temporal field appeared to be smaller than a 10 cent piece held in the nasal field of the same eye. The patient was shown a square, a circle, a triangle, a cross, two parallel lines, the figures 8 and 6 and the letter E. In every instance he recognized the object in the temporal field and drew it on paper; but every one of the objects drawn was smaller than the image perceived in the nasal field (figs. 3 and 4). This was true for each eye. Although the patient seemed to show a general micropsia on field examination, this was found to be made up of islets of micropsia intermingled with areas of blurred vision and scotomas. He also had a tendency to reverse or turn the plane of the image placed before

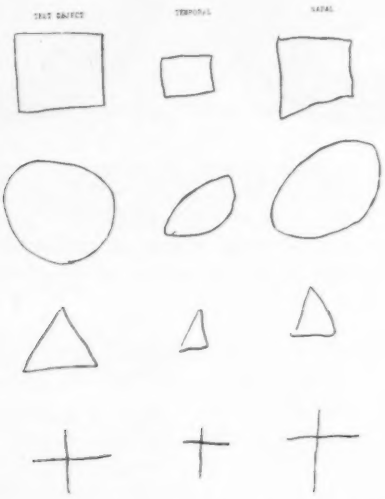

Fig. 3.—A chart illustrating what the patient saw with each field of vision. In the first column is the object shown; in the second column is the patient's drawing of the image he saw in the temporal field, and in column 3 is the image he saw in the nasal field.

him. Thus, the two parallel horizontal lines were drawn vertically, and the letter E was drawn as its mirror image (fig. 3). The letter E was reversed, or drawn as its mirror image, when seen in the nasal, or apparently normal, field. The visual acuity in the temporal fields was 10/100. He saw at 10 feet (300 cm.) a letter E which should have been recognized at 100 (300 meters).

A roentgenogram of the sella turcica and skull was normal. The spinal fluid was clear and under an initial pressure of 120 mm. of water; it contained 8 lymphocytes and a total protein content of 214 mg. per hundred cubic centimeters. The colloidal gold curve was 00000111111. The urinalysis gave negative results. The specific gravity was not fixed; the patient was able to concentrate to 1,032

per cent. The blood count was normal. The basal metabolic rate was —6 per cent. The sugar tolerance curve was found to be flat on two occasions. On one the values were as follows: initial, 60 mg. per hundred cubic centimeters; one half hour, 70 mg.; one hour, 30 mg.; two hour, 60 mg.; three hour, 35 mg.; four hour, 50 mg., and five hour, 45 mg.

An electroencephalogram showed diffuse delta activity. The lowest frequency was 3 per second, while the highest voltage was 35 microvolts. A pneumoencephalogram revealed extreme internal hydrocephalus with dilatation of all the ventricles. The configuration of the anterior portion of the third ventricle and the portion of the lateral ventricle which connect with the foramen of Monro suggested the presence of a mass in the third ventricle.

A transfrontal craniotomy on the right side disclosed a tumor in the region of the optic chiasma. Pulmonary embolism developed, and the patient died. Autopsy disclosed a large epidermoid tumor in the interpeduncular space, which compressed the chiasma and the floor of the third ventricle.

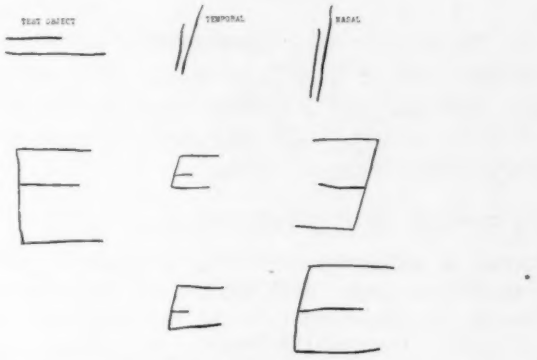

Fig. 4.—A chart illustrating the distortion of the plane of the image. Note that the horizontal lines were seen by the patient as vertical with each half-field. The micropsia is retained in the temporal field. The letter E is recorded as a mirror image when seen in the apparently normal nasal field, while there is micropsia in the temporal field. The patient realized his error and redrew the images, but again the micropsia persisted in the temporal field.

COMMENT

The limitation of the micropsia and teleopsia to the temporal fields, especially in the inferior halves, and the presence of a tumor in the chiasmal region are indubitable evidence for the peripheral origin of the optic disturbances.

It is noteworthy that the micropsia and teleopsia were localized to numerous small islands in the temporal fields. Intermingled with these were islands of blurred vision and scotomas. These findings suggest, further, that the unusual visual symptoms were due to a lesion of the

chiasma and not of the occipital cortex. Although islets of blurred vision and scotomas have been reported in association with disease of the occipital cortex (Bender and Wechsler [3]), islands of small and distant vision must be extremely rare.

The tendency to rotate the plane of the image in the nasal as well as in the temporal fields suggests visual disturbances due to disease of the occipital cortex in areas 18 and 19 of Brodmann, the centers of psychovisual integration. The turning of the plane of objects, sometimes 180 degrees, is rare even in association with lesions of the occipital lobe (Halpern [4]). In our case there was no evidence of a lesion in the parieto-occipital region. The symptom is difficult to explain.

Not all patients with scotomas in the temporal fields have micropsia and teleopsia. Special examinations of several patients with verified chiasmal lesions and incomplete bitemporal hemianopsia failed to disclose the symptoms as described in our case.

SUMMARY

A verified case of epidermoid tumor in the chiasmal region, with micropsia, teleopsia and a tendency to turn the plane of images, is reported. The micropsia and teleopsia were limited to circumscribed areas in the temporal fields of vision.

Fifth Avenue and One Hundredth Street.

3. Bender, M. B., and Wechsler, I. S.: Irregular and Multiple Homonymous Visual Field Defects, Arch. Ophth. **28**:904-912 (Nov.) 1942.

4. Halpern, F.: Kasuistischer Beitrag zur Frage des Verkehrtsehens, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:246-252 (July) 1930.

THE PSEUDOISOCHROMATIC PLATE TEST OF COLOR VISION

PRACTICAL APPLICATION

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That there is such a condition as color blindness is appreciated by most physicians. Industries have long realized the importance of good color perception, and many, such as the railroads, color printers and paint manufacturers, have made use of tests for the detection of color blindness among employees.

But what is not appreciated by many physicians is the fact that almost one out of every ten men has a deficient color sense and that the time-honored method of testing color vision in routine physical examinations by having the subject identify the colors of a half-dozen wool yarns not only is totally inadequate but indeed may be actually dangerous.

Adequate testing for deficiency in color vision is important not only to the more than 4,000 [1] American physicians devoting full or part time to industrial practice but to family physicians, who are often called on for preschool and precollege examinations, in which the disclosure of a deficiency in color vision may have a serious bearing on the student's choice of further study.

The purpose of this paper is to reassert the value of the pseudoisochromatic plate tests for color deficiency for the practical point of view, as indicated by the relation of a deficiency in color vision to color aptitude, and applies particularly to the one generally available in this country.

For the purpose of orientation a brief review of the principles of color vision is submitted.

PRINCIPLES OF COLOR VISION

Color as seen by the normal eye is appreciated or analyzed according to (1) hue, which is dependent on the spectral distribution, or

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1. Physicians in Industrial Practice, Organization Section, J. A. M. A. **116:** 1452 (March 29) 1941.

wavelength, of the light; (2) saturation, which depends on the amount of pure spectral light in the color mixture (the more saturated the color, the more pronounced the hue, variations of saturation producing various tints of the same color), and (3) luminosity, which corresponds to the intensity of the sensation and usually is considered in terms of brightness.

Any color sensation within an average range of intensities can be produced by a mixture of not more than three primary spectral colors. So far as stimuli are concerned, normal color vision is trichromatic.[2]

Disturbances of the color sense have been known as color blindness, which may be partial or total. This is an unfortunate term, since there are many variations as to degree and type. Duke-Elder stated:[2]

> A person with defective color vision may go through life quite unconscious of his inferiority and without making any incriminating mistakes, differentiating objects by their size, shape and luminosity, using all the time a complete color vocabulary based on his own experience, which teaches him that color terms are applied with great consistency to certain objects and to certain achromatic shades, until circumstances are arranged to eliminate these accessory aids and he realizes for the first time that his sensations differ from the normal.

The usual classification of color vision is based on that of Kries and Nagel:

A. Normal color vision: normal trichromasy

B. Abnormal, or defective, color vision

2. Anomalous trichromasy (perception of one or more of the three primary colors is weak)
   - (*a*) Protanomaly (red weakness—common)
   - (*b*) Deuteranomaly (green weakness—more common)
   - (*c*) Tritanomaly (blue weakness—rare)

3. Dichromasy (only colors formed by two primary colors are seen)
   - (*a*) Protanopsia (red blindness—common)
   - (*b*) Deuteranopsia (green blindness—more common)
   - (*c*) Tritanopsia (blue blindness—rare)

4. Monochromasy (the entire spectrum appears of a uniform hue—rare)

The often marked deficiencies of dichromasy are usually not difficult to detect, but, on the other hand, the relative weaknesses of anomalous trichromasy are often difficult to detect and to interpret. Wiltberger[3] spoke of anomalous trichromates as being pastel color blind. Their identification is important because they may behave as if color blind when conditions are not favorable, as when they are fatigued or are in smoke,

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2. Duke-Elder, W. S.: Textbook of Ophthalmology, London, Henry Kimpton, 1932, vol. 1.

3. Wiltberger, P. B.: Study of Color Perception and Its Practical Application to Aviation, J. Aviation Med. **10**:47-49 (March) 1939.

fog or poor light. Duke-Elder indicated that generally they rely to a greater extent than normal persons on differences in luminosity and require a higher visual angle before hue can be discriminated.

Tests for color blindness are usually considered under four headings: (1) spectrum tests, such as use of the anomaloscope of Nagel, although Edridge-Green [4] expressed the opinion that this is unsatisfactory; (2) matching tests, such as Holmgren's, although Chace [5] in 1926 stated that the yarn tests would eliminate only 50 per cent of the dangerously color blind; (3) lantern tests, which have been commonly used in testing railroad and marine workers, and (4) pseudoisochromatic plate tests, such as the Stilling, the Ishihara and the more recent Rabkin test [6] and, in this country, the test made available by the American Optical Company. Of these the pseudoisochromatic plate tests are of general value because of their availability, ease of use and relative accuracy.

Colors are called pseudoisochromatic when they are distinguished easily by normal-sighted persons but are regarded as identical by certain classes of the color blind. Rabkin described his test as a polychromatic method.

There has been considerable difference of opinion as to the relative value of the various pseudoisochromatic plate tests. Duke-Elder,[2] Tocantins and Jones,[7] Collins,[8] Clark [9] and Turner [10] expressed preference for the Ishihara test and Jennings [11] for the Stilling test. Berens and Stein [12] spoke of both the Ishihara and the Stilling as standard tests.

Although my experience with it is limited, the more recent Rabkin test, in which twenty colored plates are used, would appear to be of

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4. Edridge-Green, F. W.: The Detection of Colour-Blindness from a Practical Point of View, Proc. Roy. Soc. Med. (Sect. Ophth.) **24**:4-8 (Nov.) 1930.

5. Chace, A. E.: Color Blindness in Industry, J. A. M. A. **87**:1258-1261 (Oct. 16) 1926.

6. Rabkin, E. B.: Polychromatic Plates for Testing Color Vision, ed. 2, State Medical Publishing House of U. S. S. R., 1939.

7. Tocantins, L. M., and Jones, H. W.: Defective Color Vision and Its Handicaps in Medicine, Am. J. M. Sc. **185**:243-249 (Feb.) 1933.

8. Collins, M.: Tests in Common Use for the Diagnosis of Colour Defects, Nature, London **140**:532 (Sept. 25); 569 (Oct. 2) 1937.

9. Clark, J. H.: The Ishihara Test for Color Blindness, Am. J. Physiol. Optics **5**:269, 1924.

10. Turner, A. C.: Routine Testing of Color Vision, M. Officer **58**:90-91 (Aug. 28) 1937.

11. Jennings, J. E.: Evaluation of Pseudo-Isochromatic Tests for Detection of Color Blindness, Am. J. Ophth. **14**:952-958 (Sept.) 1931.

12. Berens, C., and Stein, L.: Group Color Vision Tests, J. A. M. A. **113**: 1563-1564 (Oct. 21) 1939.

merit, particularly because it provides more easily for the diagnosis of the type of color vision weakness. I have had no experience with the test recently devised by Wiltberger.[13]

The incidence of color blindness is generally given as 4 to 8 per cent in males and 0.4 per cent in females.[14] According to Duke-Elder, Waaler gave the following percentages: protanopsia, 0.88; protanomaly, 1.03; deuteranopsia, 1.04, and deuteranomaly, 5.06. Blue-yellow blindness is rare.

CLINICAL PROCEDURE AND DATA

In a large industrial plant 803 male workers were retested in an attempt to identify further those who might be deficient in color vision. The group comprised better than average industrial employees, since the work involved required both intelligence and ability, factors which were necessarily considered at the time of employment.

The test used was based on the pseudoisochromatic plates for testing color perception produced by the American Optical Company. This test is apparently a modification of the Stilling and Ishihara tests, and forty-six color plates are used.

All the workers were tested under the same conditions in a room shielded from daylight and lighted by ordinary daylight blue electric light bulbs. It apparently made little or no difference whether diffused daylight, ordinary electric lights or daylight blue bulbs were used, for the normal persons were just as normal under all three conditions of lighting. However, glare had to be avoided.

In giving the test, great care was taken not to count as a failure the mistaking of an 8 for a 3, a 7 for a 2 or a 6 for an 8. This is important, since such misreadings are easily made, particularly if the reader is a little careless or attempts to go too fast. The majority of persons on being cautioned and allowed to repeat will correct themselves. I considered as a failure only the gross misreading of a number or, what is more important, the inability to see any number at all.

On the basis that the truly normal person will make no errors (except with plates 33, 34 and 45, usually not read by the normal person —the actual number making no errors being 290, or 36 per cent), and that the degree of weakness in color vision increases, as do the errors, the results were arbitrarily classified as follows: (1) no impairment, 0 to 5 errors; (2) slight impairment, 6 to 10 errors; (3) moderate impairment, 11 to 20 errors, and (4) severe impairment, more than 20 errors.

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13. Wiltberger, P. B.: A New Test for the Detection of Color Blindness, Columbus, Ohio, The Warner P. Simpson Co., 1941.

14. Miles, W.: One Hundred Cases of Color Blindness Detected with the Ishihara Test, J. Gen. Psychol. **2**:535, 1929. Duke-Elder.[2]

The results of 803 examinations according to this classification were as follows: (1) no impairment, 710 persons, or 88.6 per cent; (2) slight impairment, 40, or 4.9 per cent; (3) moderate impairment, 13, or 1.6 per cent, and (4) severe impairment, 40, or 4.9 per cent.

No provision is made in the American Optical Company test for actual diagnosis of the type of color vision weakness other than the indication of red-green or blue-yellow blindness, but it is known that there are gradations from normal trichromasy through anomalous trichromasy to the more definite impairments of dichromasy, such as red and green blindness. This would seem to justify the rough numerical indication of the severity of the weakness in the pseudoisochromatic plate test.

Early in the series an attempt was made to test persons with severe weakness of color vision by giving them the Thompson modification of the Holmgren wool test. This test was soon abandoned because of frequent gross contradictions; i. e., some persons with moderate or severe impairment according to the pseudoisochromatic plate method were apparently normal according to the wool test.

When it was found that a number of men showed various degrees of impairment according to the pseudoisochromatic plate test, an attempt was made to determine the practical significance of the test. Actually a few of the workers classified as severely deficient by means of the test had long been considered by supervisors as good color men.

On the recommendation of Foss,[15] all those with weakness of color vision were given an aptitude test in an attempt to evaluate the various degrees of weakness from a practical point of view. The aptitude test has not as yet been standardized or made generally available and has not been published, pending further improvement and the accumulation of clinical data, although it has been briefly described.[16]

The test material consists of two series of colored chips of enameled metal. The chips of series I are delicately graded from a gray to a red, representing the gray axis of the protanope, so that a low score with this series would indicate protanopsia. The chips of series II are graded from the same gray to a red-purple on the gray axis of the deuterope, so that a low score with this series would indicate deuteranopsia. The color gradations are uniform as tested by spectrophotometric methods and vary only in hue, the brightness of series I appearing constant to the protanope although varying a little to the normal person and the brightness of series II appearing constant to both the normal person and the deuteranope.

15. Foss, C. E., Vice-Chairman, Inter-Society Color Council, Washington, D. C.: Personal communication to the author.

16. New Tests for Color Blindness, Science Service, May 26-June 1, 1941.

In taking the test the subject has placed before him series I, consisting of forty colored chips arranged in random order in several rows. He is then required to match with these, one at a time, a group of 20 associated chips, which are identical in color with every second gradation. Each chip is identified on its reverse side by a code number or letter, and as the matches are made the subject records his results on paper. Then the examiner, by comparison with the code, can accurately score the result. Series II, which is of a different color range, is then given. The entire test requires an average of sixty to ninety minutes.

The rating of the result is by score; the higher the score, the better the aptitude. The scoring used was as follows for each of the twenty comparisons of each series: perfect comparison, 5 points; off by one gradation, 3 points; off by two gradations, 1 point; off by three gradations, — 1 point (subtract 1, or penalize 1 point); off by more than three gradations, — 3 points (subtract 3, or penalize 3 points).

The tests were conducted in a room shielded from daylight; a table was covered with a gray blanket, and about 3 feet (90 cm.) above it a Macbeth daylight lamp was suspended for illumination. All portions of this table, on which the chips were matched, received 50 candles of illumination.

Alternate subjects were given series II to begin with, in order to prevent lowered scores for this series caused by fatigue. At the completion of his first series the subject was given the Rabkin [6] polychromatic plate test for color vision and then proceeded immediately to the second series of the aptitude test.

To determine what score in the aptitude test should be expected of the person considered normal because of having passed the American Optical Company test, 6 men who were not concerned with color in their daily work were given the test. The resultant average score was 86 for series I and 84.5 for series II. Six normal men who were constantly using color sense in their daily work and who presumably, on the basis of experience and training, should have had superior aptitude were given the same test, with an average score for series I of 83.5 and for series II of 86.5. This would seem to indicate that experience makes little difference in the measure of aptitude by the chip test or, what is more likely, that the group was too small to be significant in this respect. However, it indicates that good scores would range in the 80's.

Of the original 93 men who had been classed as having deficient color vision, 71, because of the relative importance of their work, were further tested by the Rabkin and by the aptitude test, with the results shown in the accompanying table.

Results of Rabkin and Aptitude Tests of 71 Men Whose Color Vision Was Deficient According to the American Optical Company Test

Number	Number of American Optical Company Plates Missed	Number of Blue-Yellow American Optical Company Plates Missed	Number of Rabkin Plates Missed	Rabkin Test Diagnosis	Aptitude Test Score, Series I	Aptitude Test Score, Series II	Aptitude Test Score, Average
				Group with Slight Impairment			
1	6	1	2	Anomalous trichromasy	58	60	
2	6	1	0	.....	66	54	
3	6	0	0	.....	68	70	68
4	6	0	1	Anomalous trichromasy	86	82	
5	6	2	2	Anomalous trichromasy	78	66	
6	7	1	2	Anomalous trichromasy	66	72	
7	7	2	0	.....	82	58	
8	7	2	0	.....	84	82	78
9	7	1	1	Anomalous trichromasy	84	82	
10	7	2	0	.....	90	80	
11	8	1	1	Anomalous trichromasy	66	48	
12	8	2	2	Anomalous trichromasy	66	72	
13	8	2	0	.....	66	62	67
14	8	2	0	.....	74	62	
15	8	1	0	.....	66	78	
16	8	2	5	Deuteranomaly.....	64	80	
17	9	2	2	Anomalous trichromasy	50	58	
18	9	1	0	.....	70	64	
19	9	2	1	Anomalous trichromasy	76	54	
20	9	2	4	Deuteranomaly.....	72	78	75
21	9	2	0	.....	84	68	
22	9	1	0	Anomalous trichromasy	72	82	
23	9	4	3	Anomalous trichromasy	80	78	
24	9	2	0	.....	94	84	
25	10	1	0	.....	78	78	80
26	10	3	0	.....	78	86	
				Group with Moderate Impairment			
27	11	3	1	Anomalous trichromasy	76	54	
28	11	1	0	.....	78	78	
29	11	2	0	.....	80	80	
30	11	3	0	.....	80	90	70
31	11	3	0	.....	56	36	
32	11	1	3	Anomalous trichromasy	74	60	
33	11	4	9	Deuteranomaly.....	70	75	
34	13	3	0	.....	66	58	67
35	13	2	3	Anomalous trichromasy	68	76	
36	14	4	5	Deuteranomaly.....	52	54	53
37	15	2	9	Deuteranomaly.....	80	82	81
				Group with Severe Impairment			
38	21	6	14	Deuteranopsia.....	52	36	
39	21	6	13	Protanomaly.....	54	−31	41
40	21	6	6	Deuteranomaly.....	78	60	
41	22	5	12	Deuteranomaly.....	32	40	34
42	23	6	5	Deuteranomaly.....	58	58	63
43	23	6	5	Deuteranomaly.....	70	64	
44	24	6	13	Deuteranomaly.....	82	65	
45	24	6	11	Deuteranomaly.....	80	32	53
46	24	6	14	Deuteranomaly.....	62	2	
47	25	5	13	Deuteranomaly.....	64	−18	41
48	25	6	11	Protanomaly.....	70	60	
49	27	5	14	Deuteranopsia.....	40	−18	11
50	28	6	11	Deuteranomaly.....	64	58	50
51	28	6	13	Deuteranomaly.....	58	22	
52	30	6	11	Protanomaly.....	14	8	
53	30	6	9	Deuteranomaly.....	54	−15	39
54	30	6	13	Protanomaly.....	48	56	
55	31	5	14	Deuteranopsia.....	60	14	
56	31	6	13	Protanomaly.....	22	42	25
57	31	6	13	Deuteranomaly.....	38	−22	
58	33	6	14	Deuteranopsia.....	40	−30	
59	33	6	13	Deuteranomaly.....	40	−8	8
60	33	6	13	Deuteranomaly.....	20	−12	
61	34	6	13	Deuteranomaly.....	62	−2	30
62	35	6	14	Deuteranopsia.....	34	0	
63	35	6	15	Deuteranomaly.....	42	−30	
64	35	6	15	Deuteranomaly.....	44	−4	20
65	35	6	17	Protanopsia.....	−22	22	
66	35	6	9	Deuteranomaly.....	50	70	
67	37	6	13	Protanomaly.....	−26	12	
68	37	6	13	Deuteranomaly.....	45	−2	9
69	37	6	14	Deuteranopsia.....	34	−5	
70	39	6	15	Protanopsia.....	42	−34	4
71	40	6	13	Deuteranomaly.....	72	32	51

COMMENT

In considering the original group of 93, or 11.4 per cent, classified as deficient in color vision according to the American Optical Company test, it is interesting to note that there were as many with mild impairment (4.9 per cent) as there were with severe impairment (4.9 per cent) according to the arbitrary classification and that those with moderate impairment comprised only 1.6 per cent. This would suggest that a person who is deficient in color vision is likely to be either slightly deficient or markedly so, and, although the explanation is not clear, this would seem to be in accordance with Rabkin's [6] observation that there are several degrees of anomalous trichromasy, from extremely anomalous trichromasy, or subdichromasy, to mild trichromasy, approaching normal trichromasy, which is much more common.

It is unfortunate that the entire group of men deficient in color vision could not be further studied, but the 71 who were showed a rather significant parallel in the three tests. This is evident in the subgroup with severe impairment, practically all of whom showed marked impairment with the Rabkin test as well as a pronounced deficiency in color aptitude.

In the subgroup considered to have moderate impairment, the relationship continued, although one began to see exceptions. For example, subject 37, who missed fifteen American Optical Company plates, also missed nine Rabkin plates but was good in practical work, as was indicated by his aptitude score. Subject 31 had moderate impairment according to the American Optical Company test, which was missed entirely by the Rabkin test, and he was poor in practical work, as was indicated by his aptitude score, the results tending to confirm the impression that the American Optical Company test is the more sensitive of the two pseudoisochromatic plate tests in revealing weakness of color vision.

It must be remembered that when the relation of color aptitude to color vision is considered there are four groups:

I. Persons with perfect color vision and good aptitude. This group comprises the great majority of persons with normal color vision. It is reasonable to expect that color training, experience and education would result in improved aptitude, although an improvement was not indicated by the small standardizing series of the present study.

II. Persons with perfect color vision and poor aptitude. No data are available, but such persons are probably not common.

III. Persons with deficient color vision and good aptitude. Such persons are not infrequent (e. g., subjects 4, 8, 9, 10, 24, 29, 30 and 37), but are the exception and not the rule and are mainly among those with slightly deficient color vision.

IV. Persons with deficient color vision and poor aptitude. Practically all of those whose color vision is severely deficient according to the American Optical Company test will be in this group.

Considering the group with slightly deficient color vision according to the American Optical Company test, one sees a parallel slight impairment in aptitude and a slight impairment in color vision according to the Rabkin test. That the Rabkin test is not as sensitive as the American Optical Company test is suggested by the number of mild impairments completely missed by the former. From a practical point of view, persons with slight impairment of color vision may be considered to have fair color aptitude, which is probably sufficient for ordinary color work, although they cannot be trusted under adverse conditions or for work that requires superior judgment of colors.

Persons with moderate impairment should be regarded with suspicion for any work requiring good color vision. Those with serious impairment of color vision are totally inadequate.

In the classification of the type of deficiency according to the Rabkin plates, many of the men with only a few errors were indicated as having anomalous trichromasy (unclassified), because of insufficient indication for a more definite diagnosis.

Among the men with severe deficiency whose American Optical Company and Rabkin tests gave results in complete agreement, there was more anomalous trichromasy (deuteranomaly and protanomaly) than pure dichromasy (deuteranopsia and protanopsia), and those with deuteranomaly (55.8 per cent) and deuteranopsia (20.5 per cent) outnumbered those with protanomaly (17.7 per cent) and protanopsia (5.8 per cent), respectively. These results agree generally with those of other reports, but the series was too small to establish significant percentages.

A word of caution must be said concerning the use of the six plates in the American Optical Company test designed to indicate the rare blue-yellow blindness. These plates were missed routinely by persons with serious impairment and to a less extent by those with moderate and slight impairment. Obviously, errors in the reading of these plates would be considered significant only if they were the only errors or, at least, formed the majority of the total errors.

With regard to pseudoisochromatic plate tests in general, a factor of considerable importance is that they can be properly given by an examiner who has weak color vision, for it is known that, as in the general population, the vision of almost one of every ten physicians is color deficient to some degree. Weakness of color vision in an examiner would be a source of considerable error in certain matching tests, such as the yarn tests. In addition, since the numbers on the various plates are large and easily seen, the question of lowered visual acuity—unless severe—may be disregarded as a possible source of error.

SUMMARY

1. Eight hundred and three men were tested for impairment of color vision by means of the pseudoisochromatic plates for testing color perception. Of these, 93, or 11.4 per cent, were found to have deficient color vision, and 71 were further tested.

2. Impairment of color vision as indicated by this test may be classified according to the number of errors as slight, moderate and severe. The incidence of these degrees of impairment was found to be: slight, 4.9 per cent; moderate, 1.6 per cent; severe, 4.9 per cent.

3. In general, on the basis of relative color aptitude, and from a practical point of view, persons with slight impairment of color vision may be considered satisfactory for ordinary color work, although they should not be trusted under adverse conditions or for work requiring superior judgment of colors. Those with moderate impairment should be regarded with suspicion for work requiring good color vision. Those with severe impairment are probably totally inadequate.

4. The test with pseudoisochromatic plates gives a relatively sensitive indication of the severity of the impairment of color vision.

5. The ease and rapidity of the test make it particularly valuable as a method of routine testing.

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DIABETIC RETINOSIS IN THE CHINESE

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The pathogenesis of diabetic retinosis has been a subject of much controversy since the first description of the condition, by Jaeger, in 1856. There has always been a question whether the diabetes itself gives rise to the rather characteristic fundus picture or whether the retinal changes are due to a complicating nephritis, hypertension, arteriosclerosis or other disease accompanying the diabetes.

Among the Chinese, hypertension and arteriosclerosis are much less frequent than in the West, and diabetes seems to be less severe, with less tendency to acidosis, owing rather to the difference in diet (mainly in cereals and vegetables) than to racial differences. The difference in the manifestation of these diseases, which seem to be important factors in the development of diabetic retinosis, suggested that interesting results might be obtained from an analysis of the records of Chinese diabetic patients in the Peiping Union Medical College Hospital.

On record are 183 diabetic patients whose fundi were examined, and among these 49 were found to have had diabetic retinosis, an incidence of 26.4 per cent. This figure does not accurately represent the incidence of the disease in general, because only patients whose fundi were examined and only hospitalized patients were chosen for study. Compared with an average (13 per cent) taken from reports on large numbers of patients, my percentage is on the high side.

The average duration of the diabetes before the onset of the retinosis was about seven years.

The age distribution of the patients is shown by the table (figures in parentheses). The figures agree with those generally reported in the literature.

The sex distribution showed no significant difference, 30 per cent of the male and 23 per cent of the female diabetic patients having retinosis. The difference was only 7 ± 7.43. (The error mentioned in this article is always the mean, or standard, error.)

FUNDUS PICTURE

Diabetic retinosis with deep round hemorrhages and white patches, absence of edema of the disk and the retina and a mild degree or absence of sclerosis of the retinal vessels is recognized as a disease entity. The typical fundus picture is so characteristic as to establish the diagnosis. There are, however, many atypical cases in which it is impossible to distinguish the retinosis definitely from nephritic, hypertensive or arteriosclerotic retinosis. In these cases probably other factors, such as impairment of the renal function, hypertension or arteriosclerosis, may be partly responsible for the retinosis in addition to the diabetes. Therefore the fundus picture may be conveniently classified as of two types: (1) diabetic retinosis, with the typical picture, the diabetes apparently being the only cause, and (2) retinosis in diabetes, with an atypical fundus picture due to other additional factors, as mentioned.

Among the 49 patients with retinosis, 22 showed the typical fundus picture and at the same time had no hypertension, no impairment of the renal function and no sclerosis of the retinal vessels.

The substance of this article formed part of a thesis for the degree of Doctor of Medicine granted by the Peiping Union Medical College.

PATHOGENESIS

Various factors which usually are thought to have some etiologic relation to the development of diabetic retinosis, such as the components of the diabetic metabolism, renal diseases, hypertension and arteriosclerosis, were also studied.

In connection with the diabetic metabolism, one must consider mainly hyperglycemia and the content in the blood of acetone bodies and cholesterol.

The high blood sugar content, being the cardinal sign of diabetes, was necessarily suspected of being the cause of the retinosis; however, clinical experience and also careful study of cases (Braun,[1] Hanum[2]) did not confirm this assumption. The retinosis usually occurs in association with mild diabetes in older persons, while it is almost never found with severe juvenile diabetes and a high blood sugar content.

The value considered for the blood sugar during fasting was that taken on the first day of hospitalization, before the patient was put on a diet. When this was around 100 mg. per hundred cubic centimeters, impairment of the dextrose tolerance showed the presence of diabetes. The average value for the patients with retinosis was found to be 209 mg. per hundred cubic centimeters, while that for the patients without retinosis was only 174 mg. The difference, therefore,

Age Distribution According to the Blood Sugar Content (in Milligrams per Hundred Cubic Centimeters)

Age Groups	Patients With Retinosis	Patients Without Retinosis
0-10	.....	74 (1)*
10-19	.....	279 (2)
20-29	.....	173 (3)
30-39	307 (1)	185 (21)
40-49	193 (11)	165 (33)
50-59	218 (28)	179 (40)
60-69	185 (9)	164 (22)
70-79	.....	209 (3)

* The figures in parentheses indicate the number of cases in the respective groups.

was 35 ± 14.87. As this difference between the averages was not quite significant, the z test was applied to the values presented by the different age groups, as shown in the table, and it appeared that the patients with retinosis had a significantly higher blood sugar content than the patients without retinosis. For the first time figures are here presented which suggest that a high blood sugar content is really an important etiologic factor in the development of the retinosis. In what way the increased blood sugar acts on the retina, it is difficult to say. It probably acts indirectly by damaging the blood vessels, since both the exudates and the hemorrhages are vascular in origin. (Mori[3] found glycogen deposits in the walls of the capillaries; Elwyn[4] stated the belief that the high blood sugar content produces dilatation of the capillaries, which gives rise to a circulatory disturbance, "peristasis," eventually followed by exudation and hemorrhages.)

To explain the fact that retinosis hardly ever occurs in young patients with severe diabetes (a high blood sugar level) one must remember that it takes a long time for the retinosis to develop, and young patients either succumb to the disease before the retinosis develops or their blood sugar content is brought down by insulin, the damaging agent being thus decreased. Furthermore, the blood vessels

1. Braun, R.: Arch. f. Ophth. **136**:256, 1936; Zentralbl. f. d. ges. Ophth. **38**:65, 1937.
2. Hanum, S.: Diabetic Retinitis, Copenhagen, Elmer Munksgaard, 1939.
3. Mori, S.: Acta Soc. ophth. jap. **34**:12, 1930; cited by Hanum.
4. Elwyn, H.: Problem of Diabetic Retinitis, Arch. Ophth. **25**:139 (Jan.) 1941.

of young persons are much more resistant to damage than those of older persons, in whom they are already physiologically deteriorated.

A high blood sugar content, which is evidently an important factor in the development of diabetic retinosis, in causing damage to the capillary system, is important in the pathology of diabetes as a whole. It may be assumed that, like the retinal capillaries, the other capillaries and small vessels of the body are damaged after a certain length of time by the high blood sugar content. This may, for instance, explain the tendency to gangrene in diabetic patients. It is interesting that patients with diabetic gangrene almost always have retinosis.

The occurrence of acetone bodies, which is characteristic of the diabetic metabolism, was also thought to be responsible for the development of retinosis. However, this could never be confirmed by careful clinical observations (Grafe,[5] Gray,[6] Hanum [2] and others). Only the content of acetone or of diacetic acid in the urine had been determined as a routine, and no figures for acetone bodies in the blood were available. The analysis showed that the percentage of acetonuria was even higher for the patients without retinosis (28.6 per cent) than for those with retinosis (26.4 per cent).

Hypercholesteremia is a frequent finding in diabetes, and since lipoid deposits are occasionally found by histologic examination in the white patches of the retinosis, the high cholesterol content of the blood was brought into relation to the retinosis. However, the investigation showed no remarkable difference in blood cholesterol content between patients with and those without retinosis. The reports (Bessière,[7] Waite and Beetham [8]), however, may be too few for the drawing of definite conclusions. The cholesterol content was determined for only 37 of the patients without and 14 of those with retinosis. The average value for the first group was 246 mg. and for the second 206 mg. These figures confirm only the hypothesis that there is a tendency to hyperlipemia in diabetic patients in general (the amount of cholesterol being taken as an indicator of the total amount of lipoids).

RENAL DISEASES

The fundus picture produced by chronic nephritis is sometimes difficult to distinguish from that in diabetes, and this fact, together with a frequent finding of albuminuria, is the reason that time and again a renal lesion accompanying diabetes has been made responsible for a fundus change. The more recent investigations (Hanum [2] and others), in which careful tests of the renal function were performed, showed that in the majority of cases of diabetic retinosis the kidneys worked normally. In the material under discussion, the nonprotein nitrogen content and the carbon dioxide–combining power of the blood were determined, and a phenolsulfonphthalein test of the renal function, a routine examination of the urine for albumin and sediment and, finally, in some of the cases, a urea clearance test, were performed. Though not all these tests were performed in all of the cases, an impression of the renal function could be obtained by studying all the results together. As a rule a first reading for nonprotein nitrogen above 40 mg. per hundred cubic centimeters and a value for phenolsulfonphthalein below 40 per cent were considered abnormal. A positive result of the retention test, particularly if supported by a phenolsulfonphthalein or a urea clearance test, was considered the most important criterion, while albuminuria, even with red cells, in

5. Grafe, E.: Klin. Wchnschr. **2**:1216, 1923; Klin. Monatsbl. f. Augenh. **69**:841, 1923; Deutsche med. Wchnschr. **50**:1325, 1924.
6. Gray, W. A.: Tr. Ophth. Soc. U. Kingdom **51**:108, 1931; Brit. J. Ophth. **17**:577, 1933.
7. Bessière, E.: Arch. d'opht. **49**:219, 1932.
8. Waite, J. H., and Beetham, W. P.: New England J. Med. **212**:367 and 429, 1935.

cases in which the nonprotein nitrogen content and the results of the phenolsulfonphthalein test were normal, was not considered significant enough to label the case as one with impaired renal function.

Among the 49 patients with retinosis, 9 (18.36 per cent) had impaired renal function, and among the 134 without retinosis, 17 (12.68 per cent). The difference (5.68) is less than its mean error (6.23), which indicates that it has no statistical significance. The retinosis is, therefore, probably not due to a renal factor.

HYPERTENSION AND ARTERIOSCLEROSIS

Either hypertension or arteriosclerosis alone may produce a fundus picture similar to that of diabetic retinosis, and these two diseases frequently accompany diabetes. The opinion in the literature about their importance as causes of the retinosis in diabetes is divided.

The incidence of hypertension in association with diabetic retinosis varies from 100 per cent (Volhard [9]) to 50 per cent (Heinsius [10]), and the occurrence of a normal blood pressure with this disease is frequently stressed. In the material of this study the reading taken the second day of hospitalization was used in order to eliminate too high readings due to nervous excitement on the day of admission. Since definite figures and not only the absence or presence of hypertension were wanted, the systolic reading, being more significant for hypertension, was chosen. A diastolic pressure of 90 mm. of mercury and above was considered to reveal hypertension, independently of the systolic reading. No determinations of the pressure in the central retinal artery were done.

Of the patients with retinosis (49) 12, or 24.5 per cent, had hypertension, and among the 134 without retinosis, 34, or 25.4 per cent. Evidently there was no difference in the incidence of hypertension between these two groups. The average height of the hypertension (diastolic pressure) was 105 mm. for the patients with retinosis and 99 mm. for those without. The difference of 6 ± 4.68 is not significant, and it may be assumed that hypertension is not an important factor for the development of the retinosis of diabetes.

It is an old clinical observation that arteriosclerosis as a "wear and tear disease" occurs most frequently and earlier in diabetic patients. After the age of 40 it is about twice as frequent in diabetic as in normal persons. The retinosis was brought into relationship with arteriosclerosis because it also occurs after the age of 40, and, moreover, the results both of ophthalmoscopic and of histologic examination suggest a vascular (capillary) origin of the lesions. Ophthalmoscopically, the lesions are small and not in relation to the larger vessels; histologically, thickening or glycogen infiltration of the intima of the small vessels and capillaries was observed (Mori,[8] Staupendahl,[11] Agatston [12]). These lesions, however, cannot be seen with the ophthalmoscope; what are only the changes in the larger retinal vessels are observed. Hanum [2] stated the belief that the finding of sclerosis of the visible retinal vessels does not mean that the capillaries are affected by the same process, and vice versa. Therefore, arteriosclerosis in the large vessels would not give any information about the importance of this disease in the development of the retinosis of diabetes. In the absence of histologic proof for this opinion, however, it may be better to assume that the arteriosclerotic process in the visible vessels

9. Volhard, F.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:422, 1921.

10. Heinsius, E.: Klin. Monatsbl. f. Augenh. **100**:207, 1938.

11. Staupendahl, W.: Ueber einen Fall von Glaucoma hämorrhagicum bei Diabetes mellitus mit pathologisch-anatomischem Befund, Thesis, Heidelberg, P. Braus, 1928.

12. Agatston, S. A.: Clinicopathologic Study of Diabetic Retinitis, Arch. Ophth. **24**:252 (Aug.) 1940.

goes hand in hand with that in the capillaries. It would be important to study in a large material the relationship between the ophthalmoscopically visible lesions in the larger vessels and the microscopically detectable changes in the capillary system.

Some authors have reported arteriosclerotic changes of the vessels in the majority of their cases of diabetic retinosis (Onfray,[13] Doggart,[14] Van Heuven and Hulst,[15] Foster Moore[16] and others). On the other hand, some (Folk and Soskin,[17] Madders and Miller,[18] Gray[6] and Braun[1] have supported the old opinion of Leber,[19] who said that changes in the retinal vessels are usually absent in diabetic retinosis and occur only when the retinosis is far advanced and they may be of secondary origin.

Among the patients under discussion there was no significant difference in the incidence (about 43 per cent) of retinal arteriosclerosis between those with and those without retinosis.

In spite of the differences mentioned at the beginning of this article, the data presented agree on the whole with those generally reported in the literature, except for the finding of a higher blood sugar content in Chinese diabetic patients with retinosis than in those without.

SUMMARY AND CONCLUSION

The question of the causation of diabetic retinosis is still undecided, and the present study was made in order to contribute more observations in the field. Among 183 Chinese patients with diabetes, 49 had diabetic retinosis. The age group with the highest incidence was between 50 and 60, and the average duration of the diabetes before the onset of the retinosis was about seven years. The incidence for males and for females was not significantly different.

Of the various factors which might be of etiologic importance, the blood sugar content was found to be significantly higher in the patients with retinosis than in those without, while there were no significant differences with regard to hypertension, arteriosclerosis, acetone bodies, cholesterol and impairment of renal function.

Knowing that the lesions of diabetic retinosis are most likely of vascular (capillary) origin, one may assume that an increased blood sugar content persisting over a long period damages the capillaries and thus indirectly is the cause of the fundus changes. It would be important for the understanding of diabetes in general to prove by experiment this assumption, which so far is based only on a statistical study of clinical data.

13. Onfray, R.: Ann. d'ocul. **155**:533, 1918; **159**:599, 1922.
14. Doggart: Proc. Roy. Soc. Med. **24**:170, 1930.
15. Van Heuven, J. A., and Hulst, L. A.: Nederl. tijdschr. v. geneesk. **76**:5025, 1932.
16. Moore, R. F.: Tr. Ophth. Soc. U. Kingdom **40**:15, 1920.
17. Folk, M. L., and Soskin, S.: Am. J. Ophth. **18**:432, 1935.
18. Madders and Miller: Brit. M. J. **2**:559, 1930.
19. Leber, T.: Arch. f. Ophth. **21**:206, 1875.

ORIGIN AND PATHOGENICITY OF PSEUDOMONAS PYOCYANEA IN CONJUNCTIVAL SAC

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The "bacillus of blue pus" has been recognized for many years as a pathogenic agent capable of involving the eye. In 1899 Bietti [1] described a case of rapidly spreading corneal ulcer due to this organism. Since then similar cases have been noted by many authors.[2] The bacillus is described as attacking principally the corneal stroma.[3] The organism enters through a primary break in the corneal epithelium. An ulcer forms. From this site the bacillus spreads along the layers of the stroma. The invaded area becomes infiltrated with polymorphonuclear cells, and this process continues until the ulcer is surrounded by a corneal ring abscess. A hypopyon may be present, and perforation with development of panophthalmitis can follow.

Other types of corneal involvement have been described. Funaishi [4] recorded 6 cases of ulcers at the border of a trachomatous pannus from which a pyocyaneus-like organism was recovered, and Herbert [5] described a case of punctate keratitis in which cultures of material from the conjunctival sac yielded Pseudomonas pyocyanea.

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1. Bietti, A.: Il bacillo piocianico nel cheratoipopio, Ann. di ottal. **28**:508, 1899.

2. Verderame, F.: Ueber die Infection des Auges durch den Bacillus pyocyaneus, Centralbl. f. Bakt. (Abt. 1) **58**:302, 1911. Joy, H. H.: Treatment of Experimental Bacillus Pyocyaneus Ulcer of Cornea with Sulfapyridine, Arch. Ophth. **27**:1135 (June) 1942.

3. Šafář, K.: Zur Pathogenese der Pyocyaneusinfection der Hornhaut, Ztschr. f. Augenh. **58**:269, 1926; **61**:25, 1927. Löhlein, W.: Experimentelle Untersuchungen zur Keratitisfrage, Arch. f. Augenh. **96**:265, 1925. Lanou, W. W.: Bacillus Pyocyaneus Infection of the Eye, Am. J. Ophth. **18**:950, 1935. Morelli, E.: Contributo allo studio del cherato-ipopion da bacillo piocianico, Arch. di ottal. **29**:285, 1922; abstracted, Zentralbl. f. d. ges. Ophth. **9**:225, 1923. Jackson, E., and Hartman, F. W.: Experimental Bacillus Pyocyaneus Keratitis, J. Lab. & Clin. Med. **12**:442, 1927.

4. Funaishi, S.: Sechs Fälle von Ulcus corneae durch Bacillus fluorescens, Zentralbl. f. d. ges. Ophth. **6**:349, 1922.

5. Herbert, H.: Superficial Punctate Keratitis Associated with an Encapsulated Bacillus, Ophth. Rev. **20**:339, 1901.

The organism has also been found causing other infections about the eye. Sattler [6] described panophthalmitis due to Ps. pyocyanea, and Motolese [7] investigated this condition in rabbits. Terson [8] noted a case of Ps. pyocyanea dacryocystitis. Meyer and Roeling [9] found the bacillus in a case of orbital abscess and meningitis. Brown Pusey [10] recorded 2 cases of conjunctivitis, and Derby [11] described a case of conjunctivitis with swelling of the meibomian glands in which cultures of conjunctival material showed Ps. pyocyanea.

Recently, at Vanderbilt Clinic, a case of meibomitis was observed in which the glandular expressions showed a gram-negative rod on smear and a pure growth of Ps. pyocyanea on culture. This case stimulated investigation into the factors involved in corneal and conjunctival infection by Ps. pyocyanea. The work has proceeded along the following lines: (1) a review of the possible sources of the bacillus in the eye, which led to an examination for contamination by Ps. pyocyanea of the various solutions used routinely in ocular therapy; (2) a study of the effect of patching in the presence of Ps. pyocyanea in the conjunctival sac; (3) a study of the toxicity of the organism, and (4) an investigation of its susceptibility to chemotherapy.

ORIGIN OF PS. PYOCYANEA IN THE EYE

According to the literature the presence of Ps. pyocyanea in the eye may be traced to three possible sources:

1. It is well known that Ps. pyocyanea may be present in solutions used as eye drops. Contamination of fluorescein solution has been known to occur; Wilson [12] mentioned contamination of cocaine solution,

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6. Sattler, H.: Ueber Bacillenpanophthalmitis, Ber. ü. d. Versamml. d. ophth. Gesellsch. **21**:201, 1891; **22**:156, 1892.

7. Motolese, A.: L'azione patogena del bacillus pyocyaneus sui tessuti oculari del coniglio, Boll. d'ocul. **16**:1245, 1937.

8. Terson, A., cited by Jaulin, M.: Sur la tuberculose de l'appareil lacrymal, Thesis, Paris, no. 399, 1895, and Cuénod, A.: Deux cas de dacryocystite ozéneuse; examen bacteriologique, Arch. d'opht. **14**:495, 1894.

9. Meyer, M. F., and Roeling, J. C.: Orbital Abscess with Meningitis and Recovery, Arch. Ophth. **13**:445 (March) 1935.

10. Pusey, B.: Conjunctivitis Associated with Bacillus Pyocyaneus in an Adult: Bacillus Pyocyaneus Found in a Normal Conjunctival Sac, Arch. Ophth. **37**:683, 1908.

11. Derby, G. S.: The Bacillus Pyocyaneus Found in a Case of Conjunctivitis, Am. J. Ophth. **22**:1, 1905.

12. Wilson, W. J., in Bensted, H. J., and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1929, vol. 4, p. 334.

and Shrewsbury [13] reported the development of Ps. pyocyanea meningitis after the intrathecal injection of nupercaine solution.

2. The bacillus may occur as part of the flora of the normal eye. Herbert and Mauresburg [14] found the organism in a small percentage of normal eyes, and Herbert pointed out that it is more likely to occur in a dirty person's eye. The organism is commonly found in feces and has also been demonstrated on the skin, particularly in the axillary, inguinal and perineal regions. Eberth [15] cultured it from sweat. Under these circumstances it is not surprisnig that it should occasionally be found in the eye.

3. The bacillus may be present in the eye in association with a Ps. pyocyanea infection elsewhere in the body. Browning [16] reported the cultivation of Ps. pyocyanea in material from the conjunctival sac in a case in which there was otitis media due to this organism. It has also been known to cause infections of the skin, middle and external ear, nose, mouth, palate, bronchi, intestine, urethra, ureter, prostate, testicles, gallbladder, joints, meninges and lung and to be a common cause of infection of burns.[17]

A search of the bacteriologic data in about 5,000 case records of ocular disease observed at the Institute of Ophthalmology and Vanderbilt Clinic yielded 18 cases in which Ps. pyocyanea had been demonstrated on culture of conjunctival material. These 18 cases were reviewed in an effort to find out whether the disease was related to the use of contaminated drops or was associated with Ps. pyocyanea infection in another part of the body. The results of this examination are recorded in table 1. It will be seen that in 5 of the 18 cases, or 28 per cent, eye drops contaminated with Ps. pyocyanea had been used. Contaminated physostigmine solution had been used in 4 of these and contaminated fluorescein solution in 1. In 12 cases, in 3 of which contaminated drops had been used, the organism was demonstrated but once. It was found several or many times in the remaining 6 cases and in 5 of the 6 appeared to be responsible for ocular disease, as follows:

13. Shrewsbury, J. F. D.: Bacillus Pyocyaneus Meningitis with Recovery, Brit. M. J. **1**:280, 1934.

14. Herbert, I. M. S.: Superficial Punctate Keratitis Associated with an Encapsulated Bacillus, Ophth. Rev. **20**:339, 1901. Mauresberg: Hypopyonkeratis hervorgerufen durch den Bacillus pyocyaneus, Ztschr. f. Augenh. **24**:299, 1910.

15. Eberth, C. J.: Die Bakterien im Schweiss, Virchows Arch. f. path. Anat. **62**:504, 1875.

16. Browning, S. H.: Hypopyon Ulcer, Tr. Ophth. Soc. U. Kingdom **47**:38, 1927.

17. Waite, H. H.: A Contribution to the Study of Pyocyaneus Infections, with a Report of Two Rare Cases, J. Infect. Dis. **5**:542, 1908. Lode, A.: Bacillus pyocyaneus, in Kolle, W.; Maus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1927, vol. 6, no. 5, p. 149. Fraenkel, E.: Weitere Untersuchungen über die Menschenpathogenität des Bacillus pyocyaneus, Ztschr. f. Hyg. u. Infektionskr. **84**:369, 1917.

corneal ulcer, 2 cases; endophthalmitis following iridectomy, 1 case; meibomitis, 1 case, and infection after trephining, 1 case. In the case of meibomitis and that of infection after trephining, contaminated drops had been used.

TABLE 1.—*Source of Ps. Pyocyanea in the Eye and Its Role in Ocular Disease*

Case	Patient	Diagnosis	Times Ps. Pyocyanea Found	Source of Ps. Pyocyanea	Role of Ps. Pyocyanea in the Case
1	C. B.	Herpetic keratitis	Once	Not known	Stray contaminant
2	F. C.	Aniridia, glaucoma	Once	Contaminated physostigmine salicylate solution	Contaminant from physostigmine salicylate solution
3	H. W.	Staphylococcic blepharo-conjunctivitis	Once	Not known	Stray contaminant
4	A. W.	Staphylococcic blepharo-conjunctivitis	Once	Not known	Stray contaminant
5	P. R.	Staphylococcic blepharo-conjunctivitis	Once	Not known	Stray contaminant
6	R. W.	Vernal catarrh	Once	Not known	Stray contaminant
7	A. D.	Keratoconjunctivitis, cause unknown	Once	Not known	Stray contaminant
8	M. B.	Glaucoma	Once	Contaminated physostigmine salicylate solution	Contaminant from physostigmine salicylate solution
9	A. K.	Keratitis sicca	Several times	Not known	Not known
10	A. K.	Corneal ulcer	Once	Not known	Stray contaminant
11	R. H.	Recurrent hordeola	Once	Not known	Stray contaminant
12	M. S.	Absolute glaucoma, hypopyon ulcer, endophthalmitis	Many times	Not known	Cause of ulcer
13	J. K.	Cataract, endophthalmitis	Many times	Not known	Cause of endophthalmitis following iridectomy
14	G. D.	Ps. pyocyanea meibomitis, Friedländer bacillus meibomitis, Friedländer bacillus corneal ulcer	Many times	Bed received contaminated fluorescein solution	Cause of meibomitis
15	M. H.	Glaucoma, infection after trephining	Many times	Contaminated physostigmine salicylate solution used previously	Cause of infection after trephining
16	M. P.	Glaucoma	Once	Contaminated physostigmine salicylate solution	Contaminant from physostigmine salicylate solution
17	B. C.	Staphylococcic blepharo-conjunctivitis	Once	Not known	Stray contaminant
18	M. T.	Corneal ulcer, endophthalmitis	Several times	Not known	Cause of ulcer

The case of meibomitis appears to be unique. Cases have been reported of Friedländer bacillus meibomitis, but the association of Ps. pyocyanea with the condition has not been mentioned in the literature.[18]

18. Landman, O.: Conjunctivitis and Purulent Inflammation of the Excretory Ducts of Meibomian Glands Caused by an Encapsulated Gram-Negative Diplobacillus, Arch. Ophth. **38**:374, 1909. Stiefbold, E.: Ueber einen seltenen Bakterienbefund im Sekret der Meibomischen Drüsen bei Conjunctivitis Meibomiana,

(Footnote continued on next page)

A trephined eye is probably particularly susceptible to infection with Ps. pyocyanea, and the finding of a case in which infection occurred through the use of contaminated drops serves to emphasize the importance of eliminating this source of infection.

One patient was admitted to the hospital about 6 p. m. with a diagnosis of acute bilateral glaucoma. She received physostigmine salicylate solution in both eyes every hour during the night. Next morning cultures of material from each conjunctiva and of the physostigmine solution showed Ps. pyocyanea. The medication was changed to pilocarpine hydrochloride solution, and later that day the patient was operated on. No complicating infection developed.

In no case was there an associated infection with Ps. pyocyanea elsewhere in the body.

SURVEY OF CONTAMINATION OF EYE DROPS

Cultures were made of samples from all bottles of ophthalmic solutions in use in the hospital. An occasional bottle of pontocaine hydrochloride, pilocarpine hydrochloride, ethylmorphine hydrochloride, scopolamine hydrobromide and atropine sulfate solution, and all the bottles of physostigmine salicylate 0.5 per cent and 1 per cent and of fluorescein 2 per cent solution, were found to be contaminated with Ps. pyocyanea. The pharmacy stocks of the last three solutions also yielded positive cultures.

Repeated cultures of these solutions have been made since the original survey, and it has been found that if the pharmacy stock solution does not contain Ps. pyocyanea the solutions in the wards and in the clinic are not likely to become contaminated. Accidental contamination of a single bottle has been rare. Since the solutions are changed frequently, such an isolated contamination would normally be quickly eliminated.

Klin. Monatsbl. f. Augenh. **89**:643, 1932. Wirth, M.: Ueber die chronische Eiterung der Meibomischen Drüsen, Arch. f. Augenh. **94**:73, 1924. Moklakoff, A. A.: Zur Bacteriologie der chronischen eiterigen Entzündung der Glandulae Meibomii des Lides, ibid. **43**:10, 1901. Castelain, D.: Infection particulière du bord libre palpébral (Streptothricose meibomienne), Ann. d'ocul. **138**:261, 1907. Reitsch, W.: Die chronisch-eitrige Entzündung der Meibomischen Drüsen durch Kapselbazillen, Klin. Monatsbl. f. Augenh. **49** (2 pt.):461, 1911. Chang, S. P.: A Special Form of Keratitis Caused by Friedländer's Pneumobacillus, Arch. Ophth. **19**:103 (Jan.) 1938. Cosenza, G.: Un caso di inflammazione cronica e dilatazione cri.ica simmetrica delle ghiandole del Meibomio, Boll. d'ocul. **8**:1090, 1929; abstracted, Zentralbl. f. d. ges. Ophth. **22**:624, 1930. Otuka, J.: Ueber die chronische Entzündung der Meibomischen Drüsen durch B. pneumoniae Friedländer, ibid. **40**:661, 1938. Hendriksen, S. D.: Fall von chronisch eitriger Entzündung in den Meibomischen Drüsen durch Kapselbacillen, ibid. **31**:150, 1934.

Samples for culture were taken from the solutions on hand in six ophthalmologists' private offices. Of all these solutions only the physostigmine salicylate solution in one bottle was found to contain Ps. pyocyanea.

In these culture studies physostigmine salicylate solution was the one most often found to be contaminated. This finding is contrary to common experience, which has shown fluorescein solution the one most frequently involved. It was noted that if a solution contained Ps. pyocyanea it nearly always yielded a pure culture of the bacillus. This observation was consistent with the established fact that this organism produces antibacterial agents.[19] It has been known to kill Escherichia coli in drinking water [20] and may well exert a similar bactericidal action in ophthalmic solutions.

EXPERIMENTAL STERILIZATION OF OPHTHALMIC SOLUTIONS

Fluorescein.—The ability of chlorobutanol, merthiolate and metaphen to keep a 2 per cent solution of fluorescein free from contamination was tested in the following manner:

> The fluorescein solution was prepared with various amounts of the antiseptics. One drop of a twenty-four hour broth culture of Ps. pyocyanea was then added to 5 cc. of each of the preparations. They were kept at room temperature and streaked on agar plates at the end of twenty-four hours and each day thereafter. Antisepsis was accepted when the twenty-four hour plate and all subsequent plates showed no growth.

Solutions containing merthiolate 1:20,000, metaphen 1:7,000 and chlorobutanol 0.3 per cent were freed from Ps. pyocyanea, while those containing merthiolate 1:25,000, metaphen 1:8,000 and chlorobutanol 0.2 per cent were not. In view of these results chlorobutanol was added to the hospital pontocaine hydrochloride, fluorescein and physostigmine salicylate solutions. Since then Ps. pyocyanea has not appeared in the fluorescein or in the pontocaine hydrochloride solution, but the physostigmine salicylate solution remained contaminated. There have been occasional complaints of irritation from these solutions since the addition of the chlorobutanol. Merthiolate and metaphen could have been used but contain mercury, which might cause an occasional sensitivity reaction.

Physostigmine Salicylate.—The ability of chlorobutanol, merthiolate and metaphen to free a 0.5 per cent solution of physostigmine salicylate

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19. Schoental, R.: The Nature of the Antibacterial Agents Present in Pseudomonas Pyocyanea Cultures, Brit. J. Exper. Path. **22**:137, 1941.

20. Rochaix, A., and Vieux, G.: Antagonisme du bacillus pyocyanique et du colibacille dans l'eau d'alimentation, Compt. rend. Soc. de biol. **124**:1118, 1937.

of Ps. pyocyanea was then tested by adding various amounts of the antiseptics to the contaminated hospital solution. The preparations were left at room temperature and plates streaked from them at the end of twenty-four hours and repeatedly after that.

Chlorobutanol slightly increased the acidity of the physostigmine salicylate solution but in concentrations up to 0.5 per cent did not clear it of Ps. pyocyanea. Preparations containing merthiolate 1:10,000 and metaphen 1:3,000 still showed Ps. pyocyanea after one week, but merthiolate 1:7,000 and metaphen 1:2,000 were effective.

Boiling the contaminated physostigmine salicylate solution for five minutes was also found to be effective. This is probably the most satisfactory way to treat physostigmine salicylate solution and perhaps the other solutions as well.

PRESERVATION OF PHYSOSTIGMINE SALICYLATE SOLUTION

Salicylic acid has been used in Vienna [21] to prevent physostigmine salicylate solution from turning red. It is believed to act by making the solution acid. Sodium bisulfite is used in epinephrine hydrochloride solution and in proprietary solutions for the same purpose. It too increases the solution's acidity, but it may also act as a reducing agent to prevent the red color from appearing.

In the present study physostigmine salicylate solution was found to turn slightly red on boiling. Solutions standing in dropper bottles at room temperature in the clinic turned markedly red by the end of two weeks. Solutions that were contaminated with Ps. pyocyanea turned red sooner and colored more deeply than sterile solutions. Both salicylic acid 0.1 per cent and sodium bisulfite 0.1 per cent kept the physostigmine solution colorless on boiling. The clinic solution with sodium bisulfite 0.1 per cent added was only faintly red after five weeks. An old solution of physostigmine salicylate which had already turned red became paler when sodium bisulfite 0.1 per cent was added.

Potency tests according to the method of Orzechowski and Hundrieser [22] were performed on the physostigmine solutions. In these tests the change in the size of the mouse's pupil produced by small subcutaneous injections of the drug serves as an indicator. Colorless physostigmine solution which had been preserved with sodium bisulfite was compared with the same physostigmine solution without sodium bisulfite which had turned red after seven weeks' aging. The red

21. von Sallmann, L.: Personal communication to the author.

22. Orzechowski, G., and Hundrieser, M.: Vergleichende Untersuchungen über Genalkaloide und entsprechende Alkaloide, Klin. Wchnschr. **15**:481, 1936.

physostigmine solution produced less reaction in the mouse's pupil than the colorless solution. The following tabulation is a characteristic sample of the results. The pupillary diameter is given in arbitrary units:

	Normal Pupil		0.005 Mg. of Old Physostigmine Salicylate		0.005 Mg. of Physostigmine Salicylate plus Sodium Bisulfite	
	R.	L.	R.	L.	R.	L.
Mouse 14	4	3½	4	3½		
Mouse 15	4½	4			3½	2½

The acidity of the solutions was measured with the Beckman p_H meter, with the following results:

	p_H
Physostigmine salicylate 0.5%	6.08
Physostigmine salicylate 0.5% + sodium bisulfite 0.1%	4.8
Physostigmine salicylate 0.5% + sodium bisulfite 0.2%	4.1
Physostigmine salicylate 0.5% + salicylic acid 0.1%	3.1
Physostigmine salicylate 0.5% + sodium bisulfite 0.2% + chlorobutanol 0.5%	3.5

EFFECT OF PATCHING IN THE PRESENCE OF PS. PYOCYANEA IN THE RABBIT'S EYE

In an effort to determine the effect of a patch on the ability of Ps. pyocyanea to produce conjunctivitis and corneal ulcers in the rabbit's eye, six series of 12 rabbits each were tested as follows:

Series 1: Several drops of Ps. pyocyanea suspension were instilled into the conjunctival sac.

Series 2: The cornea was scratched and a drop of the suspension instilled.

Series 3: The cornea was scratched, a drop of the suspension instilled and the eye patched.

Series 4: A drop of suspension was instilled and the eye patched.

Series 5: The cornea was scratched and the eye patched.

Series 6: The eye was patched without any corneal scratch or instillation.

The suspension was made by mixing 8 cc. of physiologic solution of sodium chloride with a culture of Ps. pyocyanea grown on a blood agar slant for twenty-four hours. The eyes were patched by bridging the two lids with a strip of cotton gauze soaked in collodion. The corneal abrasions were made with a no. 27 hypodermic needle. The epithelium was dug away in the manner in which one might remove a foreign body. The patches were removed at the end of forty-eight hours and the eyes examined. They were examined again at the end of ninety-six hours and frequently thereafter.

The results are shown in table 2, the first column giving the type of procedure followed and the subsequent columns the number of animals and the severity of the conjunctival and corneal reactions. A survey of the table reveals that Ps. pyocyanea did not produce inflammation in normal rabbits' conjunctival sacs but that if a patch was applied, a

conjunctivitis and a blepharitis were regularly found to be present after forty-eight hours. When the cornea was abraded and Ps. pyocyanea instilled, the presence of a patch definitely increased the intensity and severity of the corneal involvement; the eyes that were patched always showed a marked conjunctivitis, whereas the eyes that were not patched showed a conjunctivitis corresponding in intensity to the extent of the corneal involvement.

Conjunctival material was taken for culture when the animals were examined. Ps. pyocyanea was not isolated from unpatched eyes but was found in pure culture in material from every eye that had been patched. However, forty-eight hours after the patches were removed only an occasional colony of the organism was recoverable on culture. This was true even though a corneal ulcer and infiltration had developed.

TABLE 2.—*Effect of Patching in the Presence of Ps. Pyocyanea in the Rabbit's Eye*

Procedure	Conjunctivitis			Corneal Ulcer			Total
	—	+	4+	—	+	4+	
Ps. pyocyanea instilled	12	..	..	12	..	..	12
Cornea scratched and Ps. pyocyanea instilled	8	2	2	8	2	2	12
Cornea scratched, Ps. pyocyanea instilled and eye patched	..	..	12	..	7	5	12
Ps. pyocyanea instilled and eye patched	..	..	12	12	..	..	12
Controls:							
Cornea scratched and eye patched	9	1	2	11	1	..	12
Eye patched	9	1	2	12	..	..	12

In one of the two control series normal rabbits' eyes were merely patched; in the other the eyes were patched after the cornea had been scratched. The majority of these eyes showed no reaction at the end of forty-eight hours, but there were a few that showed a conjunctivitis and 1, among those whose corneas were scratched, that showed a mild corneal reaction. The patch seemed to facilitate the propagation of any organism that happened to be in the conjunctival sac. From most eyes showing a conjunctivitis, cultures of conjunctival material were found to be loaded with hemolytic, mannitol-fermenting Staphylococcus albus. In one instance a pure culture of Ps. pyocyanea was obtained although no bacilli had been instilled into the eye.

Although these results should not be assumed to apply to man, the old dictum "never patch an eye that is discharging" [23] and the familiar test of patching an eye to bring out a bacterial infection indicate that clinical experience has shown the effects of patching to be similar in man.

23. Rea, R. L.: Affections of the Eye in General Practice, Caduceus **8**:1, 1929.

TOXICITY OF PS. PYOCYANEA

Although Ps. pyocyanea has never been found as an intracellular epithelial parasite,[24] it has been described in the literature as producing a toxin,[25] hydrocyanic acid [26] and several bactericidal substances.[19] Morax and Elmassian [27] in 1899 showed that filtrates of cultures of staphylococci, gonococci, diplobacilli and Corynebacterium diphtheriae repeatedly instilled into the rabbit's conjunctival sac produced a conjunctivitis in two to four hours. In an effort to test the toxicity of Ps. pyocyanea, an attempt was made to repeat this experiment with filtrates of the organism in question.

The bacillus was grown in plain broth for five days at room temperature. This suspension was then filtered through a Berkefeld filter. The filtrate was instilled into a rabbit's conjunctival sac every ten minutes. An unfiltered broth culture of Ps. pyocyanea and sterile plain broth were used as controls.

The eyes receiving the Ps. pyocyanea culture and those receiving the filtered material showed, in two and a half hours, conjunctivitis with hyperemia, edema and a purulent discharge. The eyes treated with sterile plain broth remained unchanged.

The same procedure was followed with contaminated physostigmine salicylate solution taken from the hospital bottles. Sterile physostigmine solution was used as a control. The contaminated solution had turned red; the sterile solution was colorless. Each of 2 rabbits received the contaminated material in one eye and the sterile material in the other eye.

At the end of two and a half hours the eyes which had received the contaminated material showed slight hyperemia, conjunctival edema and a slight mucopurulent discharge. At the end of three and a half hours the reaction in the eyes which had received the contaminated drops was more severe, while the other eyes appeared unchanged.

These results suggest that toxic material from the bacilli lying on the lids and in the conjunctival sac is probably responsible for Ps. pyocyanea conjunctivitis and that bacterial invasion is probably not a factor.

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24. Lindner, K.: Zur Topographie der parasitären Bindehautkeime, Arch. f. Ophth. **105**:778, 1921.

25. Axenfeld, T.: The Bacteriology of the Eye, translated by A. Macnab, London, Baillière, Tindall & Cox, 1908. Jackson, E., and Hartman, F. W.: Experimental Bacillus Pyocyaneus Keratitis, J. Lab. & Clin. Med. **12**:442, 1927. Miyashita, S.: Immunität gegen Bacillus pyocyaneus, Zentralbl. f. d. ges. Ophth. **9**:197, 1923. Oesterlin, E. J.: Experimental Studies with Pyocyaneus Filtrates, J. Immunol. **16**:359, 1929. Wassermann, A.: Experimentelle Untersuchungen über einige theoretische Punkte der Immunitätslehre, Ztschr. f. Hyg. u. Infektionskr. **22**:263, 1896.

26. Patty, F. A.: The Production of Hydrocyanic Acid by Bacillus Pyocyaneus, J. Infect. Dis. **29**:73, 1921.

27. Morax, V., and Elmassian: Du rôle des toxines dans la production des inflammations de la conjonctive, Ann. d'ocul. **122**:81, 1899.

EFFECT OF CHEMOTHERAPY ON PS. PYOCYANEA

The action of five of the sulfonamide compounds on the growth of Ps. pyocyanea was tested in vitro on three strains of the bacillus.

Equimolar broth solutions of sulfanilamide, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine), nitrosulfanilamide and nitrosulfathiazole were pipetted into test tubes, 4.5 cc. into each. Control tubes contained 4.5 cc. of plain broth. Serial dilutions of a twenty-four hour broth culture of the organism to be tested were added in 0.5 cc. amounts to each tube. These tubes were then incubated at 37 C. and examined at frequent intervals for cloudiness. The effect of the various drugs on the organism was indicated by the length of time the appearance of cloudiness was retarded; the longer the cloudiness was prevented the greater the drug's effectiveness.

The following tabulation is a characteristic protocol, the degree of cloudiness being indicated as plus to 4 plus:

Dilution of Bacillus 10^{-6}	Concentration of Drug, Twentieth-Molar							
	Hr. 9	Hr. 16	Hr. 20	Hr. 23	Hr. 28	Hr. 40	Hr. 48	Hr. 56
Control	—	2+	4+	4+	4+	4+	4+	4+
Sulfanilamide	—	—	—	—	4+	4+	4+	4+
Sulfathiazole	—	—	—	—	—	2+	3+	3+
Sulfadiazine	—	—	—	—	—	3+	4+	4+
Nitrosulfanilamide	—	—	3+	4+	4+	4+	4+	4+
Nitrosulfathiazole	—	—	2+	2+	4+	4+	4+	4+

It was found that sulfathiazole and sulfadiazine were the most effective drugs, sulfanilamide and nitrosulfathiazole next in order and nitrosulfanilamide the least effective.

Such in vitro tests serve only to indicate the drugs most likely to have clinical value. In a case of severe corneal infection, sulfadiazine given by mouth, applied locally as a powder and administered by iontophoresis would probably give the highest corneal concentration.

SUMMARY AND CONCLUSIONS

1. The records of 18 cases of ocular disease in which Ps. pyocyanea had been demonstrated on conjunctival culture were reviewed in an effort to trace the source of the bacillus in the eye. In 5 cases the disease was found to be associated with the use of contaminated eye drops, physostigmine salicylate solution in 4 instances and fluorescein solution in 1. In the other cases the source was assumed to be the patient's own body or environment, as no other indications were found. No patient showed an associated infection elsewhere in the body.

2. In 5 of the 18 cases Ps. pyocyanea appeared to be the cause of ocular disease, as follows: corneal ulcer, 2 cases; endophthalmitis

following iridectomy, 1 case; meibomitis, 1 case, and infection after trephining, 1 case. The meibomitis and the infection after trephining occurred in cases in which contaminated drops had been used.

3. Cultures of solutions commonly used as eye drops showed that physostigmine salicylate solution is the preparation most likely to be contaminated with Ps. pyocyanea. The bacillus was usually found in pure culture and may be presumed to exert an inhibitory effect on other bacterial growth.

4. Tests of the power of various antiseptics to keep the solutions free from Ps. pyocyanea showed that considerably higher concentrations are needed to sterilize physostigmine salicylate than to sterilize fluorescein. Boiling the solutions and changing them frequently appears to be the most satisfactory way to assure sterility.

5. The addition of a small amount of sodium bisulfite prevented physostigmine salicylate solution from turning red.

6. Six series of rabbits' eyes were tested for the effect of patching on the ability of Ps. pyocyanea to produce conjunctivitis and corneal ulcers. Patching was found to be necessary for the production of conjunctivitis and if the cornea was abraded to increase the incidence and severity of corneal invasion. The organism could not be recovered from unpatched eyes but was found in pure culture in material from every eye that had been patched.

7. A filtrate of a Ps. pyocyanea culture produced a severe conjunctivitis when instilled into rabbits' conjunctival sacs, suggesting that toxic material released by the bacilli rather than bacterial invasion is probably responsible for Ps. pyocyanea conjunctivitis.

8. In vitro tests of several sulfonamide compounds showed sulfathiazole and sulfadiazine to be the most effective against Ps. pyocyanea of those tested.

Dr. C. L. Fox outlined the chemotherapy experiment; Dr. J. L. Boyd did the potency tests on physostigmine salicylate solutions, and Dr. Phillips Thygeson gave assistance and guidance at all stages of the work.

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ADIE'S SYNDROME

REPORT OF TWO CASES

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The presence in healthy persons of one myotonic pupil associated with a disturbance or absence of one or more of the deep tendon reflexes is neither a recent discovery nor a rare condition. As long ago as 1902, Saenger [1] and Strasburger [2] independently published descriptions of this symptom complex, and in 1906 Markus [3] reported a case in which it occurred in a boy 12 years of age; but it was more than twenty-five years later before the disorder, now called by the name Adie's syndrome, was generally accorded the serious attention either of ophthalmologists or of neurologists. Even today the pathogenesis [4] of this condition is not understood and unanimity as to its clinical importance is lacking. Errors in diagnosis are not unusual. The most frequent mistake has been to regard the myotonic pupil, with its concomitant symptoms, as a manifestation of syphilis of the central nervous system, an irregular type of the Argyll Robertson pupil, and time has made but little change in this attitude. Such a diagnosis is at least convenient and in many cases has been assumed even in the absence of positive serologic findings and other corroborative evidence. Case 1 is an example of this type of inaccurate diagnosis. In view of the known facts such failures are reprehensible and must be condemned, for, in addition to a social upheaval in the patient's life, they are apt to cause the adoption of prolonged, expensive and needless, if not harmful, therapeutic measures. I believe, therefore, that all cases of Adie's syndrome wherever found should be brought to the attention of the medical profession with as much publicity as possible, and this is my principal reason for publishing the records of these 2 cases.

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1. Saenger, A.: Ueber myotonische Pupillenbenegung, Neurol. Centralbl. **21**: 837-839, 1902.

2. Strasburger, J.: Pupillenträgheit bei Akkomodation und Convergenz. Neurol. Centralbl. **21**:1388 and 1052, 1902.

3. Markus, C.: Notes on a Peculiar Pupil Phenomenon in a Case of Partial Iridoplegia, Tr. Ophth. Soc. U. Kingdom **26**:50-58, 1906.

4. Heersema, P. H., and Moersch, F. P.: Adie's Syndrome, Proc. Staff Meet. Mayo Clin. **14**:17-22, 1939. Gardner, W. J., and Shively, F. I., Jr.: Adie's Syndrome: Report of Four Cases, Cleveland Clin. Quart. **7**:203-208, 1940.

NATURE OF THE MYOTONIC PUPIL

In 1931 Adie [5] published a lecture entitled "Argyll-Robertson Pupils, True and False," and a year later he described the presence of a myotonic pupil as a disorder *sui generis*.[6] About that time Holmes [7] presented cases similar to Adie's before the Ophthalmological Society of the United Kingdom. After these reports appeared the benign nature of the myotonic pupil became more generally accepted, and in 1936 Bramwell [8] suggested the name Homes-Adie syndrome, which has at times been employed. Before, a syphilitic antecedent had usually been taken for granted, and the affected pupil was for the most part regarded as a phase of the Argyll Robertson pupil, but it now appears to be definitely established that the two conditions are in no way related. The myotonic pupil, usually present in one eye only, sometimes oval or irregular in shape, nearly always larger than its fellow, is occasionally widely dilated. It may be partially or wholly inactive to light and incompletely or entirely indifferent to convergence and to accommodation. During convergence, contraction may be delayed for several seconds, but, when once started, it sometimes continues until the affected pupil has gradually become smaller than its fellow, continuing even after convergence has been relaxed. If the patient remains for an hour or so in a dark room the pupils may dilate to an equal size, but when the myotonic pupil is again subjected to an intense light, after a short delay, it will contract slowly and at times become smaller that it was before it dilated in darkness.[5] There are cases, however, such as case 1, in which it appears to be impossible to detect any response whatever either to light or to accommodation.

The two conditions may coexist, but that syphilis is a harbinger of Adie's syndrome has not yet been established. As a causative agent this disease seems to have been ruled out completely, and the presence of a myotonic pupil, whether a disease entity or merely a symptom of some deep-seated disturbance, the nature of which is not now understood, appears to be neither inimical to good health nor adverse to longevity. Persons have been known to exhibit this symptom complex for a period of almost a half of a century,[9] living well into senescence.

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5. Adie, W. J.: Argyll-Robertson Pupils, True and False, Brit. M. J. **2**:136-138, 1931.

6. Adie, W. J.: Tonic Pupils and Absent Reflexes: A Benign Disorder Sui Generis; Its Complete and Incomplete Forms, Brain **55**:98-113, 1932.

7. Holmes, G.: Partial Iridoplegia Associated with Symptoms of Other Diseases of the Nervous System, Tr. Ophth. Soc. U. Kingdom **51**:209-228, 1931.

8. Bramwell, E.: The Holmes-Adie Syndrome: A Benign Clinical Entity Which Simulates Syphilis of the Nervous System, Edinburgh M. J. **43**:83-92, 1936.

9. (*a*) Weber, F. P.: Dr. Markus's Original Case of Markus's Syndrome, Proc. Roy. Soc. Med. **26**:530-531, 1933. (*b*) Rudolph, G. de M.: Tonic Pupils with Absent Tendon Reflexes in Mother and Daughter, J. Neurol. & Psychopath. **16**:367-368, 1936. (*c*) Moore, R. F.: Tr. Ophth. Soc. U. Kingdom **44**:38, 1924.

It is usually encountered in early adult life, but McKinney and Frocht [10] reported it in a child 3 years of age. Females are more frequently affected than males. Often one or more of the deep tendon reflexes, especially the ankle jerk, is absent or deficient. The affected pupil is never miotic, but it is occasionally smaller than its fellow.[10] The findings are variable and may differ from time to time in the same person. The typical myotonic pupil usually responds readily to miotics and mydriatics. Subjective symptoms are few and for the most part of little importance. Occasionally there is a complaint of spontaneous, though slight, ocular pains and slight blurring of vision. Adie included in his description several atypical forms, such as (*a*) tonic pupillary reaction alone, (*b*) atypical phase of the tonic pupil alone (usually mistaken for iridoplegia or internal ophthalmoplegia), (*c*) atypical pupils with absense of tendon reflexes and (*d*) absence of tendon reflexes alone.

NATURE OF THE ARGYLL ROBERTSON PUPIL

The Argyll Robertson pupil, on the other hand, is nearly always found in both eyes and is never dilated. It is easy to diagnose, but the absence of the light reflex alone, with retention of the ability of the pupil to contract during accommodation, is not sufficient evidence for the establishment of the diagnosis. Miosis is a characteristic and must be present if the diagnosis is to be accepted. Adie's contention that this type of pupil is infallible evidence of syphilis is not a hasty conclusion lacking the support of well established clinical data, for it has been abundantly substantiated by the known facts in many cases. Argyll Robertson pupils are, therefore, an unfavorable prognostic sign, occurring more frequently in men than in women and for the most part in middle or later life. These miotic pupils, sometimes irregular in outline, often unequal in diameter, seldom if ever dilate readily and completely in respnose to a mydriatic.

ETIOLOGY

The etiologic basis of Adie's syndrome is in the speculative stage. Adie described the syndrome as a manifestation of a disorder of the vegetative nervous system, an expression of a kind of perversion of nervous activity of which at present there is no conception, a disorder *sui generis*. It has been observed in several members of the same family, including twins,[11] and in more than two generations.[9b] Ataxia, sensory disturbances and atrophy of the optic nerve, which are commonly associated with the Argyll Robertson pupil, are no part of Adie's syndrome,

10. McKinney, J. M., and Frocht, M.: Adie's Syndrome: A Non-Luetic Disease Simulating Tabes Dorsalis, Am. J. M. Sc. **199**:546-555, 1940.

11. Hough, W. H.: Adie's Syndrome in Twins: A Preliminary Report, M. Ann. District of Columbia **10**:137-140, 1941.

nor is this condition known to be related to myotonia congenita or Thomsen's disease. The attempt has been made to explain the myotonic pupil with its accompanying disturbances on the basis of an unstable nervous system. Adie stated the belief that it is associated with or caused by changes in the vegetative portion of the oculomotor nucleus, but such changes do not seem to account for the disturbance in the deep tendon reflexes. The course is chronic, but the disorder is benign and may exist alone or in conjunction with other diseases without any known etiologic relationship of one to the other.

CASE 1.—A. N. A., a divorced man aged 44, was called to my attention on Oct. 3, 1941 by a neurologist [12] to whom he had applied for treatment for neurosyphilis, the diagnosis having been established by his family physician. His father had died at the age of 72 of cancer of the lip. His mother was an invalid 73 years old. He had one son, 19 years of age, of whom he knew almost nothing except that he was healthy as an infant and small child. In all other respects his family history was of no special importance.

Twenty years ago the patient was kicked in the abdomen by a horse, the injury causing him to be confined to his bed for four weeks. Recovery was complete. Eighteen months previous to examination, he had injured his head while standing on his hands. Since that time he had had difficulty in extending his neck, and the joints of his neck crepitated when his head was rotated on its vertical axis. He had had no other serious illness. He did not know when he could have contracted syphilis, but stated that he had had gonorrhea five years before. Although he said that at times for over three months his left eye had been slightly painful and its vision somewhat blurred, he had never worn glasses, and it was not until eight weeks prior to my interview that he realized for the first time an inequality in the diameters of his two pupils, which was called to his attention by a friend.

The left pupil was 5.5 mm. in diameter at the time of examination and firmly fixed. The right was 2.5 mm. as observed in ordinary daylight in a room with large outside windows and reacted normally in all respects. Prolonged exposure to bright artificial light or to direct sunlight failed to produce any change whatever in the size or shape of the left pupil, nor did its size or shape change after the patient remained in a completely dark room for thirty minutes. In fact, he was kept under observation for more than two weeks, during which time the left pupil remained dilated and absolutely inactive to light and accommodation. Both pupils were circular. With a mydriatic it was possible to increase the diameter of the left pupil so slightly, if at all, that the change seemed to be imaginary. The knee, ankle and cremasteric reflexes on the right side were absent. There was a surgical scar over the region of the appendix. All serologic tests, including tests of the cerebrospinal fluid, were negative for syphilis, and there were no residuals or other evidence either of syphilis or of gonorrhea. The patient, however, having been convinced by his family physician and other physicians of a diagnosis of syphilis, was naturally somewhat apprehensive and apathetic and ready to resign himself to extensive and thorough antisyphilitic treatment, although his physical condition was good and he was well nourished and well developed. His vision was good and completely correctable, as follows: right eye, 20/40, or 20/20 —1 with a

12. I had previously made a hurried routine examination of this man's eyes without recognizing the true condition.

correction of + 0.50 D. cyl., axis 150; left eye, 20/50, or 20/15 — 1 with a correction of + 0.75 D. sph. ⊃ + 0.50 D. cyl., axis 180; both eyes for near vision, add + 1.50 D. sph. The eyegrounds were normal.

The clinical picture in this case is interesting. The patient was a well nourished healthy-appearing man of middle age with the left pupil myotonic and the cremasteric, knee and ankle reflexes absent on the right side and with subjective ocular symptoms of only three months' duration. The mental attitude was perfectly natural. The patient was calm of demeanor, his spirits becoming buoyant only when he was thoroughly convinced of the benign nature of his disorder.

Case 2.—J. T. B., a man aged 55, was referred to me on Jan. 16, 1942 by a colleague for a routine examination of the eyes. He was receiving treatment for chronic bronchitis. In addition to the presence of rales and other signs of a bronchial disturbance, the ankle reflexes were absent and the patellar reflex was elicited on the right only on reenforcement, while on the left it approached more nearly the normal state. There was a pterygium on the nasal side of each eye. Both pupils were irregular in outline. The left was pear shaped. Its longer diameter was about 3.5 mm. and its shorter 2.5 mm. at the widest point. The right pupil was almost triangular, the longest side of the triangle being 6 mm. and

The eyes in case 2.

the shortest 4 mm. It reacted neither to accommodation nor to ordinary light in the usual way. The left reacted well both to light and to accommodation. When the patient was kept in a dark room for one and one-fourth hours, with all light excluded from his eyes, no change in shape or size of the right pupil occurred, but when the pupil was exposed for five minutes to an intense artificial light, it contracted slightly. Both pupils responded readily to mydriatics and miotics and under the former became perfectly circular, although the right always remained larger than the left.

The strange appearance of his pupils, the patient said, had been present for twenty years and had never at any time caused him the slightest inconvenience or annoyance. He gave no history of venereal disease and showed no evidence of such a disorder. He refused examination of his cerebrospinal fluid, but his blood showed no evidence of syphilis and his mental reactions were absolutely normal for a man of his station. The family history, as he related it, was not important. Refraction gave the following results: right eye, 20/100, or 20/20 with a correction of — 1.00 D. sph.; left eye, 20/50, or 20/20 with a correction of — 0.75 D. sph.; both eyes for near vision, + 2.00 D. sph. The eye grounds were normal.

While admitting that his eyes were objects of curiosity to the medical profession, the patient stated that their peculiar condition presented no problem as far as he himself was concerned, for annoying subjective symptoms had always been absent. A trapper by vocation, and never having worn eyeglasses, he was proud of what he considered to be his keen eyesight and exceptional marksmanship.

In this case both pupils were affected, although the left was still normally active. The disorder had been present for twenty years but had not disturbed the general health.

For the consideration of the medical profession, these 2 cases are offered for their clinical and scientific importance, with the hope that further interest in the study of Adie's syndrome may be stimulated, but my limited knowledge of the fundamental nature of this disorder warrants no specific conclusions.

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DIPLOPIA IN NARCOLEPSY

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Narcolepsy is a syndrome characterized by two elements: (*a*) brief attacks of sleep; (*b*) brief attacks of flaccid paralysis without loss of consciousness, occurring usually in response to some emotion, such as laughter or excitement, pleasant or unpleasant. When the paralysis occurs in response to emotion it is called cataplexy. It may also occur without relation to emotion. It may occur just before the patient falls asleep or just after he wakes up, a fact which will be discussed hereafter, or it may occur out of a clear sky, apparently spontaneously. The syndrome is about three times as common in men as in women and usually starts in the second or third decade. Either symptom may antedate the other, or the two may appear at about the same time. Once started, the syndrome usually persists throughout the remainder of life. In a few cases it is symptomatic of an organic disease of the brain, such as epidemic encephalitis; in the great majority it is "idiopathic." In most cases the symptoms are in abeyance so long as the patient is taking adequate amounts of benzedrine.

The pathogenesis of narcolepsy is still in dispute. Because somnolence is caused by lesions in the floor of the third ventricle, there are some authorities who suspect a disturbance of this region in narcolepsy. But disturbances in this region will not account for the attacks of paralysis.

To other workers the key to the pathogenesis of narcolepsy is furnished by Pavlov's work on cerebral inhibition. Pavlov's work deserves the most careful study, because he was able to produce sleep in animals, without drugs, merely by applying stimuli under certain conditions, in such a manner as to reveal clearly the process by which spontaneous sleep occurs. In a series of papers published elsewhere[1] I have sought to show how Pavlov's work illuminates the pathogenesis

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1. Levin, M.: (*a*) The Pathogenesis of Narcolepsy, with a Consideration of Sleep-Paralysis and Localised Sleep, J. Neurol. & Psychopath. **14**:1, 1933; (*b*) Military Aspects of Narcolepsy, with Remarks on the Pathogenesis of Narcolepsy and on Fatigue, ibid. **14**:124, 1933; (*c*) "Crowding" of Inhibition and of Excitation, ibid. **14**:345, 1934; (*d*) Narcolepsy and the Machine Age: The Recent Increase in the Incidence of Narcolepsy, ibid. **15**:60, 1934; (*e*) The Role of the Cerebral Cortex in Narcolepsy: The Classification of Narcolepsy and Allied Disorders, ibid. **15**:236, 1935; (*f*) The Pathogenesis of Cataplexy on Anger, ibid. **16**:140, 1935.

of narcolepsy, and since it is in the light of his work that one can best understand narcoleptic diplopia, a brief account of it will be given here.

PAVLOV'S WORK ON INTERNAL INHIBITION AND SLEEP

Pavlov [2] discovered that one could establish a "conditioned" reflex to a stimulus by allowing that stimulus to serve as the signal, or forerunner, of an "unconditioned" stimulus. Thus, let the animal always hear a bell (conditioned stimulus) just before he is given his meat (unconditioned stimulus), and he will in time salivate on hearing the bell. The salivary reflex in response to the bell is a "conditioned" reflex, the animal having been taught by the conditions of the experiment that the bell is the forerunner of meat. Pavlov assumed that a link is established between cerebral centers excited by the bell and those centers which effect salivation.

Production of Inhibition.—Pavlov then found that certain alterations in the experiment led to the inhibition of already established conditioned reflexes. There are four ways of producing what he called "internal inhibition": these he called extinction, conditioned inhibition, delay and differentiation.

Extinction: A conditioned reflex can be established and maintained only so long as it is "reinforced"; i. e., the conditioned stimulus must be followed by the unconditioned stimulus. After the bell must come the meat. If, the reflex having been established, the bell is no longer reinforced, it will soon cease to elicit saliva: The reflex will undergo "extinction." Pavlov assumed that the bell, which once excited the cerebral salivary centers, now causes inhibition of these centers.

Conditioned Inhibition: A conditioned reflex having been established, let the conditioned stimulus be combined with an additional stimulus, and never reinforce the combined stimulus but reinforce as always the positive conditioned stimulus when it is applied singly. For example, combine the bell with a flash of light, and never give meat after the combined stimulus, but give it as before when the bell alone is the stimulus. The animal will learn that bell alone means meat, while bell plus light means no meat, and he will, after sufficient training, salivate as he always did in response to the bell but not in response to the combined stimulus. Pavlov designated the combined stimuli as an "inhibitory combination."

Pavlov (page 75) sought to ascertain whether the phenomenon of conditioned inhibition is "really in the nature of an inhibition" or is "merely a passive disappearance of the positive conditioned reflex owing to the compound stimulus remaining habitually unreinforced." Combin-

2. Pavlov, I. P.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, London, Oxford University Press, 1927. The page numbers enclosed in parentheses in this section refer to this work.

ing the additional stimulus with an alien positive conditioned stimulus, he found (page 76) that the new combination, offered for the first time, produced almost complete disappearance of the conditioned reflex response. He therefore concluded (page 77) that "where a conditioned inhibition has been firmly established, the additional stimulus itself acquires inhibitory properties which can be manifested outside the parent combination."

Delay: This method is concerned with the time interval which separates the moment of application of the conditioned stimulus and the moment of reinforcement. When a conditioned reflex has been established in the ordinary way (the conditioned stimulus being reinforced in one to five seconds), the reflex response appears almost immediately after the conditioned stimulus. One may now progressively lengthen the time interval between stimulus and reinforcement; e. g., one may offer the meat as much as three minutes after the bell has begun to sound. As the interval is lengthened, the reflex response is delayed, so that saliva appears only after a latent period. Pavlov gave evidence (page 92) to show that the excitatory process in the cerebral salivary centers does not merely come into being at the end of the latent period; on the contrary, it is present in full force from the start of the latent period but is temporarily overcome by an inhibitory process. Thus, if during the latent period one presents some alien stimulus not hitherto associated with conditioned salivary reflexes, a copious secretion of saliva at once ensues.

Differentiation: When a conditioned reflex is established to a stimulus, say a musical tone of eight hundred double vibrations, there is an initial "period of generalization" (page 113), in which the reflex is evoked also by related stimuli, i. e. by neighboring tones. By repeatedly applying the tone 800 double vibrations with reinforcement and neighboring tones without reinforcement, it is possible (within limits) to restrict the reflex response to the former. This is called "differentiation." To show the minuteness of differentiation of which the dog is capable, it may be noted that differentiation has been established between tones of 800 and 812 double vibrations (page 136). Pavlov gave evidence (pages 125 to 130) to show that differentiation is based on inhibition: In other words, the tones, save only that which constitutes the positive conditioned stimulus, evoke an inhibitory process which holds in check the excitations which at one time all related tones aroused in the cerebral salivary centers. To give but one bit of evidence, he found that after differentiation has been established between a positive and a negative stimulus, salivation will occur if one combines the negative stimulus with an alien stimulus not hitherto associated with conditioned salivary reflexes (exactly as in the example cited under "Delay").

Spontaneous Inhibition.—Besides the four methods already given whereby internal inhibition may be intentionally produced, inhibition always develops spontaneously, even when one does not try to produce it, from the mere repetition of conditioned stimuli however regularly reinforced (page 234).[3] Such inhibition Pavlov regarded as a manifestation of "exhaustion of cortical elements as a result of their activity in response to a stimulus" (page 244). Reflexes which have become inhibited from too much exercise are granted a renewal of strength if the stimuli in question are withheld for a time. One can understand this when one considers how one's appetite for a particular food grows jaded on eating it too often.

Pavlov found that inhibition, however produced, tends to irradiate from its point of origin. Thus, when a stimulus has acquired inhibitory properties, its application produces an inhibitory after-effect which diminishes or abolishes the animal's response to unrelated positive stimuli. At the same time, seldom if ever is the entire cortex under an inhibitory spell; instead, there are excitatory processes here and there, which, with the intervening inhibitory processes, form a "mosaic" which is ever shifting and which determines what the animal does at any given moment (page 219).

Relation of Sleep to Inhibition.—The observation that is of prime importance for this study is that the methods of producing inhibition already described also produce sleep (page 251). In experiments involving these methods "drowsiness and sleep were met with continually." For example, in the experiments on differentiation Pavlov found that while he was establishing a conditioned reflex to a musical tone the animal remained alert in the course of the work, but when he undertook to establish the differentiation of a tone close to the positive one, the animal began to get drowsy and in some instances fell asleep. The method of delay gave some startling examples. In experiments with dogs involving a delay of ten or fifteen seconds, some animals remained alert during work spread over years, "but so soon as the reflex was delayed for 30 seconds drowsiness and sleep appeared . . . . The quick transition from full alertness into true physiological sleep, due to this seemingly insignificant change in the experimental conditions, is amazing" (page 252). Equally amazing are certain experiments on delay in which the animal falls asleep during the latent period (while awaiting the unconditioned stimulus) and wakes a few seconds before the moment when it has been trained to expect the unconditioned stimulus. In these cases the animal "falls asleep each time exactly at the beginning of the action of the conditioned stimulus. The eyes close, the head droops, the whole body relaxes and hangs on the loops of the

3. Dr. W. Horsley Gantt has informed me that this occurs only in certain dogs.

stand, and the animal emits an occasional snore." After the lapse of a definite period—twenty-five seconds in experiments involving a delay of thirty seconds and about two minutes in those involving a delay of three minutes—"the animal quickly and spontaneously awakens and exhibits a sharp alimentary motor and salivary response" (page 261).

Pavlov reported that his experiments abounded "with observations showing that internal inhibition invariably passes into sleep unless special precautions are taken" (page 252), and he concluded that inhibition and sleep are one and the same thing, sleep being inhibition in its final stage when it has irradiated so as to involve all or most of the cortex and possibly lower centers as well. The quantitative difference between sleep and lesser degrees of inhibition was brought out especially clearly in some experiments on differentiation (page 254):

> A tone served as the stimulus to a positive conditioned reflex, while twenty neighboring tones up and down the scale were differentiated as stimuli for negative conditioned reflexes. This animal was never inclined to drowsiness or sleep when a balance was maintained between the number of repetitions of the positive and negative conditioned stimuli, and under these conditions the dog always gave full reflexes to the applications of the positive stimulus. As soon, however, as the inhibitory tones were used several times in succession, the dog quickly fell into such a profound sleep that even most powerful extraneous stimuli failed to awaken it.

Some physicians find it hard to accept Pavlov's views on inhibition and sleep, largely, it would seem, because he used the word "inhibition" in a sense different from the ordinary. As customarily used, the word designates a function performed by inhibitory centers in consequence of their excitation. Thus, inhibition of the heart ensues on excitation of the vagus nerve. Accustomed to this use of the word, physicians are apt to be puzzled by Pavlov's views, for it is hard to reconcile sleep (obviously a resting state) with their idea of inhibition (implying excitation of inhibitory centers). It therefore must always be remembered that Pavlov used the word in another sense, to denote the state of cerebral cells when they are not excited—a state of quiescence in which either (*a*) they are recovering from the effects of excitation (as in inhibition ensuing on the constant repetition of conditioned stimuli, even when they are reinforced) or (*b*) they are quiescent because excitation would be inconsonant with the external conditions of the animal (as in the experiments on extinction, conditioned inhibition, delay and differentiation).

NARCOLEPSY IN THE LIGHT OF PAVLOV'S WORK

The significance of Pavlov's studies for human physiology lies in the fact that man, both normal and narcoleptic, tends, like the dog, to fall asleep under conditions which give rise to inhibition. Of course,

nature's experiments with man are often so complex as to defy analysis, but sometimes they can be shown to be accurate copies of Pavlov's experiments.

Sleep in Man Resulting from Conditioned Inhibition.—The sphere of conditioned inhibition offers the clearest parallel between nature's experiments with man and Pavlov's with dogs. Examples will be given of persons who fell asleep when faced with some peril or unpleasantness from which they dared not escape, and it will be shown that such situations give rise to conditioned inhibition.

(*a*) Sleep in Situations of Peril: In the war of 1914 to 1918 there were soldiers who became sleepy in the thick of battle, especially if it was their first experience of actual combat. MacCurdy,[4] enumerating the reactions of soldiers to their first bombardment, said that one of them was "lethargy so extreme that the individual will lie down and perforce to sleep with a pathological indifference to the danger." The same thing happens in civil life. Narcoleptic patients fall asleep with significant frequency in situations of peril, as when working on a scaffold or on a ladder. In an earlier paper [1b] reference was made to specific cases; since that paper was written, other cases have been reported. Thus, Daniels [5] (page 5) mentioned a narcoleptic patient who fell asleep while cutting ice on a lake. Cozby [6] reported the case of a sailor in the Navy who fell asleep while painting over the side of the ship. In case 2 of Wilson and Watson [7] the patient fell asleep while operating a machine at a mill, the kind of machine into which a workman could fall if careless.

The significance of these examples lies in the fact that, faced with a dangerous situation, the subject has to suppress his impulse to escape. The natural or unconditioned reaction to danger is to run away, but the soldier, wishing to appear brave or fearing to be shot for treason, suppresses this reaction. Here is an "inhibitory combination" consisting of these two stimuli: (1) the soldier sees menacing shells, and (2) he perceives a situation which permits no escape. If the second stimulus did not exist, the first would evoke an uninhibited escape reflex. If, for example, a civilian wandered into a zone where rock was being blasted and found himself in the midst of a shower of missiles, he would take to his heels with no compulsion to suppress the impulse. But the second stimulus, acting with the first, forms an inhibitory combination, exactly as in Pavlov's experiments on conditioned inhibition.

4. MacCurdy, J. T.: War Neuroses, Psychiatric Bull. **2**:243, 1917.

5. Daniels, L. E.: Narcolepsy, Medicine **13**:1, 1934.

6. Cozby, H. O.: Narcolepsy, U. S. Nav. M. Bull. **34**:471, 1936.

7. Wilson, D. C., and Watson, R. F.: Narcolepsy, with Special Reference to the Carotid Sinus Reflex, South. M. J. **27**:754, 1934.

Since the impulse to escape is powerful, the inhibitory process that suppresses it must be even more powerful—powerful enough to irradiate over the highest cerebral centers and cause sleep.

(*b*) Sleep During Pain: Fewer in number, but perhaps even more striking, are 3 cases in which the patient fell asleep while undergoing painful medical or dental treatment. Gowers [8] reported the case of a man who had attacks of sleep "which were induced by most varied influences. He had a nasal fistula and whenever a probe was passed down this he fell asleep." Morton [9] reported the case of a patient who fell asleep while the dentist was pounding a gold filling, and in case 2 of an early paper of mine [10] the patient fell asleep while the dentist was actually drilling a cavity. Since pain usually drives sleep away, these cases cannot be coincidences. They are open to the same explanation as those in the last paragraph but one. The natural response of the man in the dental chair would be to shove the dentist and his instrument away. This indeed is what the child does. The adult, not wishing to appear a coward, suppresses this impulse; in physiologic terms, there is an inhibitory combination of stimuli.

To be sure, not everybody falls asleep when he suppresses his defensive reflexes. It is necessary to assume that people vary in the susceptibility of the brain to inhibition and that patients with narcolepsy are unduly susceptible—suffer from undue "inhibitability" of the highest cerebral centers. Narcolepsy is thus the opposite of epilepsy, in which the brain, or more accurately some particular part of it, suffers from undue excitability.

Sleep in Man Resulting from Differentiation.—The frequency with which soldiers on sentry duty fell asleep in the war of 1914 to 1918 was largely responsible for the interest subsequently shown in narcolepsy. The task which faces the sentry is the differentiation of positive and negative stimuli. It will be remembered that Pavlov trained dogs to respond positively to a musical tone and negatively to a tone nearby on the scale. Nature does something similar to the sentry. The sentry hears a noise and gets ready to act the moment he is satisfied there is potential danger nearby. Usually the noise turns out to be unimportant, and an inhibitory process checks the incipient positive response: The sentry suppresses the impulse to sound the alarm. Each time he differentiates a negative from a positive stimulus a certain "amount" of inhibition comes into being. Let this happen a hundred times in a night,

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8. Gowers, W. R.: A Manual of Diseases of the Nervous System, London, J. & A. Churchill, 1888, vol. 2, p. 953.

9. Morton, W. J.: Presentation of Case, J. Nerv. & Ment. Dis. **11**:615, 1884.

10. Levin, M.: Narcolepsy (Gelineau's Syndrome) and Other Varieties of Morbid Somnolence, Arch. Neurol. & Psychiat. **22**:1172 (Dec.) 1929.

and the cumulative effect of the many inhibitory processes will result in sleepiness, which will be greater if the subject's highest cerebral centers are unduly inhibitable.

PARALYSIS

Thus far only the attacks of sleep in narcolepsy have been considered. Attacks of flaccid paralysis constitute the other element of the syndrome. In these attacks, which last several seconds or minutes, the patient, while conscious, is paralyzed all over. Atonia, objective and subjective, is a prominent feature. It has been noted by several physicians who have witnessed an attack.[11] Subjectively, the patient feels "limp," "limber," "as weak as a kitten" or "like a rag dropped on the floor." It will be helpful to consider those attacks which occur in relation to sleep. Sometimes an attack comes on while the patient is falling asleep; he notices suddenly that he cannot move; after several seconds or minutes the paralysis passes over into sleep (save that in some instances the paralysis is associated with anxiety, which is not conducive to sleep, and he becomes wide awake). More often the attack comes on just when the patient has waked from either a normal night's sleep or a diurnal attack of sleep; he is conscious and oriented but cannot move; after several seconds or minutes the paralysis clears up, either gradually or suddenly, and the patient is as well as ever. The former type of attack may be called "predormitial paralysis"; the latter, "postdormitial paralysis"; the two collectively, "sleep paralysis." An account has already been given of a number of interesting features of these attacks.[1a]

Sleep paralysis is enlightening because it occurs in the transition between wakefulness and sleep. As wakefulness gives way to sleep there is a gradual irradiation of inhibition from many foci scattered over the cortex; when the inhibitory processes have invaded a sufficient area of the cortex, the subject passes over into sleep. In predormitial paralysis it would seem that inhibition has invaded the motor cortex before it has sufficiently invaded the rest of the cortex, so that the patient is paralyzed while yet awake. Conversely, as sleep gives way to wakefulness, the inhibition which has been reigning in the cortex is dissipated, usually all at once. In postdormitial paralysis, instead of being dissipated all at once, it lingers for a time in the motor cortex.

In respect to muscle tone, the motor cortex gives rise to two pathways: (*a*) the pyramidal tract, which, contrary to traditional belief, does not inhibit tone but excites it, a pyramidal lesion producing flaccid palsy (Tower [12]), and (*b*) extrapyramidal pathways, which both excite and inhibit tone. In view of the flaccidity found in the paralytic attacks

11. Levin, M.: Cataplexy, Brain **55**:397, 1932.
12. Tower, S. S.: Pyramidal Lesion in the Monkey, Brain **63**:36, 1940.

of narcolepsy, one might suppose that somehow the pyramidal tract alone is affected, being subject to transitory exhaustion. But against this supposition is the completeness of the paralysis. Loss of the pyramidal tract does not interfere with those movements which are mediated by extrapyramidal paths. Tower showed that after pyramidal section the animal is still able to carry on certain primitive movements, such as grasping. In man the movements of a young infant show what one can do without the pyramidal system. Thus it is evident in the paralytic attacks of narcolepsy that the utter inability to lift a finger is more than could be accounted for by pyramidal exhaustion alone. Possibly there is exhaustion not only of cortical centers, extrapyramidal as well as pyramidal (answering to the complete immobility), but of subcortical motor centers (answering to the tonelessness). This problem, as indeed the whole problem of the physiology of narcolepsy, is still in the speculative stage.

DIPLOPIA

The problem of diplopia may now be considered. Diplopia in narcolepsy occurs under a variety of conditions, and it will be convenient to begin with those cases in which the patient sees double just before he falls asleep or just after he wakes. This may be called "sleep diplopia," in analogy with sleep paralysis.

Predormitial diplopia is a matter of everyday experience: doubtless every one has seen double just before closing his eyes in sleep. In addition, there have been reported 7 cases of narcolepsy in which the patient saw double at the beginning of some of his attacks of sleep. Five of these were in the Mayo Clinic series reported by Daniels,[5] and 1 was reported by Wohlfahrt [13] (case 2) and 1 by Ulrich [14] (case 1). Postdormitial diplopia seldom if ever is found in healthy persons but has been noted in 4 cases of narcolepsy, reported respectively by Daniels,[5] Jones,[15] Hilpert [16] and Lafora and Aydillo [17] (case 2).

These cases of sleep diplopia support the hypothesis that there is a center, or mechanism, for binocular vision, which coordinates the movements of the eyeball so as to prevent diplopia. This center may, when

13. Wohlfahrt, S.: Quelques recherches cliniques sur la narcolepsie, Acta psychiat. et neurol. **6**:277, 1931.

14. Ulrich, H.; Trapp, C. E., and Vidgoff, B.: The Treatment of Narcolepsy with Benzedrine Sulphate, Ann. Int. Med. **9**:1213, 1936.

15. Jones, M. S.: A Case of Recurrent Attacks of Prolonged Sleep, J. Neurol. & Psychopath. **16**:130, 1935.

16. Hilpert, P.: Ueber einen Fall von Narkolepsie, Klin. Wchnschr. **4**:1553, 1925.

17. Lafora, G. R., and Aydillo, N. L.: Tratiamento de la narcolepsia con la efedrina, Ann. de med. int., Madrid **1**:3, 1932; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **64**:194, 1932.

the patient is in process of falling asleep, undergo inhibition too soon, causing predormitial diplopia. Conversely, when he wakes it may remain inhibited too long, causing postdormitial diplopia.

Where is this center? Certainly it is in the cortex rather than below. The finest ocular movements, those employed in scrutinizing an object, are clearly of cortical origin. The cortex even contains centers for relatively simple ocular movements, such as conjugate movement to the side on which a light is seen; if this, a relatively crude and automatic act, is mediated by the cortex, the finer act of scrutinizing an object must beyond question be mediated there too.

While the constitution of the center for binocular vision is not understood, this much is certain, that it is not contained within a small area but, rather, is spread over a large part of the cortex, probably comprising portions of both occipital and both frontal lobes. However, since there is no visual loss as one passes into or out of sleep, it is likely that diplopia at these moments comes from inhibition of the anterior rather than of the posterior part of the center.

If these views are correct, it would seem that sleep paralysis and sleep diplopia are different manifestations of the same process, the difference being that in one it is the motor cortex and certain subcortical motor centers which appear to be inhibited, while in the other it is an oculomotor area probably anterior to the motor cortex.

Other circumstances in which diplopia occurs will now be mentioned, and in each instance an analogy will be shown with the generalized paralysis of narcolepsy.

Diplopia During Cataplexy.—A great number of patients have seen double at the onset of or during a cataplectic attack. Daniels [5] noted that in the Mayo Clinic series 11 patients had "diplopia, or blurring of vision, at the beginning of their cataplectic seizures"; presumably most, if not all, had diplopia. Cases of such diplopia were reported also by Wohlfahrt [18] (case 5), Janzen [18] (case 2), Cloake,[19] Notkin and Jelliffe [20] (case 1), Scharfetter and Seeger [21] and Palmer.[22]

If my views on narcoleptic diplopia are correct, the occurrence of diplopia at the beginning of, or in the course of, a cataplectic attack

18. Janzen, E.: Ueber Narkolepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **104:** 800, 1926.

19. Cloake, P. C. P., in discussion on Wilson, S. A. K.: The Narcolepsies, Proc. Roy. Soc. Med. **21:**1244, 1927-1928.

20. Notkin, J., and Jelliffe, S. E.: The Narcolepsies: Cryptogenic and Symptomatic Types, Arch. Neurol. & Psychiat. **31:**615 (March) 1934.

21. Scharfetter, H., and Seeger, T.: Zur Klinik der kataplektischen Anfälle, Ztschr. f. d. ges. Neurol. u. Psychiat. **153:**37, 1935.

22. Palmer, H. A.: Narcolepsy, Brit. M. J. **2:**478, 1941.

offers no problem. The only problem is how emotion-arousing stimuli produce inhibition of motor centers, a problem which need not be considered here.

Spontaneous Diplopia.—This type comprises attacks of diplopia occurring out of a clear sky, without apparent reason. Daniels [5] found 4 cases in the Mayo Clinic series. Murphy [23] reported 3 cases (cases 1, 2 and 5). Single cases were reported by Spiller [24] (case 2), Wilson [25] (case 1), Silverstein,[26] Hoff and Stengel,[27] Baxley [28] (case 1), van der Scheer [29] (case 1) and Kennedy.[30] In the last 2 cases attacks of diplopia were the first and for a time the only symptom of the disease. Thus Kennedy's patient began to have attacks of diplopia at 22, attacks of sleep at 25 and cataplexy at 26.

This type of diplopia, also, is analogous with paralysis, for paralysis too may occur spontaneously in narcolepsy. While most paralytic attacks are precipitated by emotion, there are some which occur out of a clear sky; indeed there are some patients who, in respect to paralysis, have only the spontaneous attacks.

Diplopia on Reading.—Two patients, reported on respectively by Zehrer [31] (case 2) and Daniels,[5] had diplopia on reading.

Pavlov has shown that inhibition is always arising and irradiating over the cortex, even when one is wide awake. Invasion of the motor cortex by such inhibition may be assumed as the cause of spontaneous paralytic attacks; likewise, invasion of the center for binocular vision will cause spontaneous diplopia. Reading, which taxes this center, facilitates its inhibition.

Diplopia on Warding Off an Impending Attack of Sleep.—In this type of diplopia the patient on attempting to ward off an impending attack of sleep suddenly begins to see double. Reported cases include

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23. Murphy, W. F.: Narcolepsy: A Review and Presentation of Seven Cases, Am. J. Psychiat. **98**:334, 1941.

24. Spiller, W. G.: Narcolepsy Occasionally a Post-Encephalitic Syndrome, J. A. M. A. **86**:673 (March 6) 1926.

25. Wilson, S. A. K.: The Narcolepsies, Brain **51**:63, 1928.

26. Silverstein, A.: A Case of Gelineau Syndrome, Arch. Neurol. & Psychiat. **25**:1376 (June) 1931.

27. Hoff, H., and Stengel, E.: Ueber familiäre Narkolepsie, Klin. Wchnschr. **10**:1300, 1931.

28. Baxley, H. W.: Narcolepsy, M. Bull. Vet. Admin. **12**:143, 1935.

29. van der Scheer, W. M.: Narcolepsie en cataplexie, Nederl. tijdschr. v. geneesk. **78**:5114, 1934.

30. Kennedy, A. M.: A Note on Narcolepsy, with Report of a Case, Brit. M. J. **1**:1112, 1929.

31. Zehrer, H.: Zur Klinik der Narkolepsie, Allg. Ztschr. f. Psychiat. **92**: 263, 1929.

Janzen's [18] cases 2 and 3, an unnumbered case of Daniels' [5] (page 77), Baxley's [28] case 2 and an unreported case of my own. The phenomenon can be experienced by any one who stays awake long enough.

In 1933 [1a] I alluded to the remarkable observation, made by 5 narcoleptic patients, that attempting to fight off sleep sometimes provokes an attack of paralysis. In that paper I should have included case 1 of Wenderowic [32] (1924); since it was written, 2 additional cases have been reported—case 11 of Thiele and Bernhardt [33] and 1 by Krick [34]—besides several others that are suggestive but not clearcut enough to warrant mention here. This phenomenon fits in most remarkably with Pavlov's views on inhibition and sleep. Pavlov, as has already been said, regarded the cortex as the scene of a "mosaic" of functions, with areas of inhibition here and there separated by areas of excitation, tending to keep each other in check. After a period of activity the areas of excitation diminish in extent, owing to fatigue of cortical cells, and the inhibition, opposed no longer, irradiates over the cortex, producing sleep. When one fights off sleep, excitations arise to keep inhibition in check; figuratively, and even literally, one pinches oneself. Thus a contest ensues, and the result in certain cases reminds one of what happens in a football game when the runner with the ball is crowded by his opponents into that part of the field where he sees the least opposition. In some such manner, inhibition, blocked in its progress over some parts of the cortex, is crowded aside or shunted into the motor cortex, producing an attack of paralysis.

The most remarkable instance of shunting of inhibition occurred in Cohen's [35] case 2. The patient gave the following account of one of her cataplectic attacks:

> I think I could have stopped it in the first stages, but unfortunately I was stupid enough to concentrate not on sitting still, but on trying not to spill the coffee from the cup I was holding, with the result that I kept the coffee cup quite safe, but slipped to the floor beside it.

This demonstrates in the clearest way the shunting of inhibition from one part of the brain to another—in this instance from motor centers for the arms to centers for the trunks and legs.

These cases of paralysis throw light on the mechanism of the diplopia which ensues when one wards off sleep. Inhibition when blocked in its

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32. Wenderowic, E.: Hypnolepsie (Narcolepsia Gelineau) und ihre Behandlung, Arch. f. Psychiat. **72**:459, 1924.

33. Thiele, R., and Bernhardt, H.: Beiträge zur Kenntnis der Narkolepsie, Berlin, S. Karger, 1933.

34. Krick, J. W.: Zum Problem der Narkolepsie, Allg. Ztschr. f. Psychiat. **103**:128, 1935.

35. Cohen, H.: The Treatment of Narcolepsy with Ephedrine, Lancet **2**:335, 1932.

progress over the cortex may be shunted into the center for binocular vision, just as it sometimes is shunted into motor centers.

Thus diplopia and generalized paralysis behave alike at every point, and the conclusion seems inescapable that when they occur paroxysmally in narcolepsy they are due to a common mechanism.

So far in this paper little has been said of the "sleep center" in the hypothalamus, and its relation to the present problem may now be briefly considered. To assume, as has been done, that a disturbance of the sleep center will by itself explain the phenomena of narcolepsy is to take a one-sided view of the problem of sleep and consciousness. Such a view is comparable in one-sidedness to the view that consciousness is "localized" in the hypothalamus. If anywhere, consciousness is localized in the cerebral cortex, for it is the cortex that enables one to comprehend, reason and initiate voluntary movement, and, since these functions are, with insignificant exceptions, in abeyance during sleep, it is the cortex which must be reduced to inactivity before sleep ensues. It may be objected that decorticate animals have regular cycles of sleep and wakefulness. This by no means proves that the cortex has nothing to do with the matter. Unquestionably sleep involves subcortical structures too. But when one thinks of a person asleep, the picture that comes to mind is of a person who makes few or no movements, who is unaware of the environment and whose thinking, if any, is reduced to the simplest terms—the picture, that is, of a person whose cortical function is in partial, if not complete, abeyance. The only conceivable role of the sleep center is in some way to regulate sleep, keep it within bounds. It really should be called the "waking" center or, better, the "alertness" center (since "waking" is apt to connote merely the transition between sleep and alertness); its destruction causes, not the loss of sleep, but constant unchecked sleep. In some way it must neutralize the effects of fatigue of cortical cells, thereby prolonging wakefulness and increasing the efficiency of the cortex as an adaptive instrument. In any case, it is the cortex which, so to speak, sleeps; the alertness center merely exercises a measure of control over the process.

If excessive sleep were the only symptom of narcolepsy, one might entertain the notion that the disorder arises from a weakening of the alertness center, which interferes with its regulative action on the cortex and permits the cortex to become exhausted too easily. But what in actuality renders this notion questionable is the fact that in addition to excessive sleep, signifying untimely inhibition of the whole cortex, there are symptoms signifying untimely inhibition of parts of the cortex, the commonest and best example being the attacks of flaccid paralysis. Conceivably a deranged hypothalamic alertness center might allow the cerebral cortex in toto to fall prey to exhaustion with undue ease, causing attacks of sleep, but it strains the imagination to suppose that a

derangement of this center might cause selective exhaustion of just a part of the cortex, e. g. of the motor cortex. Still, it might. In any case, one must not confuse remote and immediate causes. Inhibition of the cortex, or of parts of it, is suggested as the immediate cause of the manifestations of narcolepsy. A disturbance of the hypothalamic alertness center, interfering with its regulative action on the cortex and allowing the cortex to undergo inhibition too easily, may or may not be the remote cause.

SUMMARY

The attacks of sleep of narcolepsy occur with significant frequency under conditions duplicating those which in Pavlov's experiments elicited sleep and other manifestations of cerebral inhibition. This, together with other evidence, suggests that narcolepsy results from a disturbance (in the cerebral cortex or elsewhere) which renders the cortex unduly exhaustible or "inhibitable," the attacks of sleep arising from inhibition of the whole cortex and the attacks of flaccid paralysis from inhibition of just the motor cortex (plus, probably, certain subcortical motor centers as well). Attention is called to the frequency of attacks of diplopia in this disorder, and it is suggested that they arise from transitory inhibition of a cortical mechanism for binocular vision.

The Johns Hopkins Hospital.

RIBOFLAVIN FOR ROSACEA KERATITIS, MARGINAL CORNEAL ULCERS AND CATARRHAL CORNEAL INFILTRATES

LABORATORY AND CLINICAL STUDIES

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CLEVELAND

The term rosacea keratitis was long ago applied to a condition frequently observed in patients having acne rosacea. This condition is characterized by the presence of one or more small peripheral infiltrates, between which and the limbus a number of small capillaries appear, progressing almost to, but not quite touching, the infiltrates. It was popularized by Doggart,[1] and his descriptions and illustrations of the advanced pathologic changes have caused many ophthalmologists to consider only the advanced stage as "rosacea keratitis." It has long been observed that Negroes and other patients without dermatologic acne rosacea may have severe lesions. In fact, the incidence without acne rosacea is so much greater that the occurrence with it is now considered almost a coincidence, although in general the lesions accompanying acne rosacea are of greater severity and without the aid of riboflavin are much more destructive of the visual function.

Much smaller infiltrates, marginal at their inception and approached but never invaded by capillaries, are diagnosed superficial marginal ulcers or catarrhal ulcers by most ophthalmologists, the diagnosis depending on whether or not a conjunctival exudate and meibomitis accompany the inception of the ulcer. Identical in type of process, but not in extent or severity, these lesions have one other common factor —the immediate response to be expected by the parenteral injection of riboflavin. From the etiologic point of view, most physicians feel that dietary abuse, overindulgence in alcoholic beverages, overwork and

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1. Doggart, J. H.: Ocular Rosacea, Tr. Ophth. Soc. U. Kingdom **50**:98, 1930.

irregular lunching predispose to superficial marginal ulcers. The infiltrate of "catarrhal ulcers," following so-called catarrhal conjunctivitis, is generally considered as an indolent sterile infiltrate, probably caused by abnormal tissue metabolism, rather than by a local bacterial infection. After three or four daily intravenous injections of riboflavin, these infiltrates and the capillaries disappear, with relief of symptoms, even though a coexisting blepharoconjunctivitis remains unchanged clinically.

If one could postulate a classification of metabolic disorders of the cornea, it would be based on (1) the slit lamp appearance of small (probably sterile) infiltrates, arising near the limbus (at the arcus senilis area) and approached but not invaded by capillaries and (2) prompt response to parenteral injections of riboflavin. This group of metabolic disorders would include mild rosacea keratitis, superficial marginal ulcers and catarrhal ulcers. Rosacea keratitis tends, with remissions, to progress, frequently to the formation of the triangular opacities of Doggart, while superficial marginal ulcers usually subside in two weeks even without treatment other than the rest and dietary improvement enforced by the symptoms. Catarrhal ulcers frequently subside in the same time with treatment by means of the usual antiseptic drops or sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) ointment. In the latter two conditions, riboflavin simply reduces the duration of symptoms from one or two weeks to one or two days.

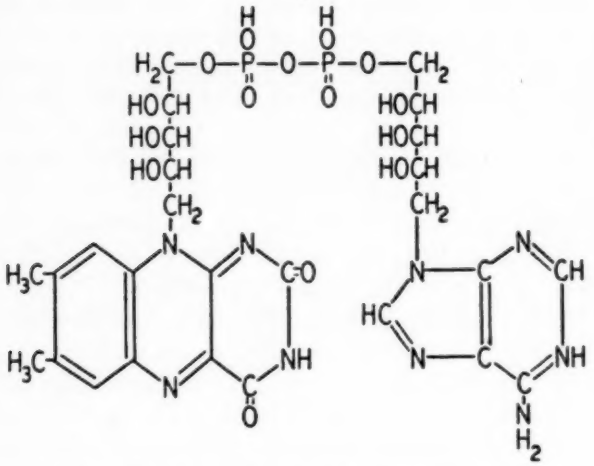
Early reports on our observations [2] concerning the use of riboflavin for the relief of so-called rosacea keratitis have been reviewed recently.[3] It has been our experience that the intravenous administration of riboflavin is more effective than the oral. We attributed the difference to a failure in absorption of the riboflavin from the gastrointestinal tract, because several of the patients who showed no clinical improvement with riboflavin administered orally showed a prompt remission when the intravenous route was used. It is now our practice to administer 1 mg. of riboflavin intravenously each day for three to four days, supplementing this with a preparation of vitamin B complex containing 830 micrograms of riboflavin per teaspoonful, administered orally, 3 teaspoonfuls daily, for about two weeks, and recommending inclusion in the diet

2. (*a*) Cole, H. N., cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939, p. 455. (*b*) Johnson, L. V., and Eckardt, R. E.: Rosacea Keratitis and Conditions with Vascularization of the Cornea Treated with Riboflavin, Arch. Ophth. **23**:899 (May) 1940; (*c*) Ocular Conditions Associated with Clinical Riboflavin Deficiency, ibid. **24**:1001 (Nov.) 1940. (*d*) Johnson, L. V.: Clinical Ocular Conditions Associated with Vitamin B-Complex Deficiencies, Am. J. Ophth. **24**:1233 (Nov.) 1941.

3. Benedict, W. L., and Wagener, H. P.: Riboflavin and Keratitis, Am. J. M. Sc. **201**:303 (Feb.) 1941. Butt, H. R.; Leary, W. V., and Wilder, R. M.: Diseases of Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **69**:277 (Feb.) 1942. Waite, J. H.: Medical Progress: Ophthalmology, New England J. Med. **226**:1023 (June 25) 1942.

of natural foodstuffs high in riboflavin, such as milk, liver and eggs. With this regimen, we have seen only 1 patient fail to respond. His case will be discussed in more detail subsequently.

Knowledge of the role of riboflavin in intermediate metabolism has been advancing with the years, so that it is now necessary to revise the concepts once held. Whereas Warburg's yellow enzyme was formerly considered to play an important role in cellular respiration, it now seems likely that if it is present at all in the animal organism its role is an insignificant one. This concept has been necessitated by its low turnover number.[4] Recently, nine riboflavin-containing enzymes have been discovered, the properties of which are more dependent on the protein with which the riboflavin-containing prosthetic group is conjugated than



Riboflavin-adenine-dinucleotide (from Hogness[5]).

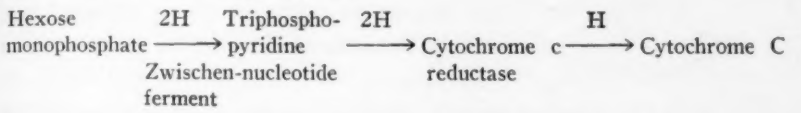
on the prosthetic group itself. These enzymes have been summarized in tabular form by Hogness.[5] The turnover number for some of them is as high as eight thousand, as compared with fifty for Warburg's yellow enzyme. It is immediately apparent that in equal quantities these enzymes can play a much larger role than Warburg's yellow enzyme in cellular respiration.

4. The turnover number of a substance may be defined as the number of times per minute that it can accept hydrogen from the substrate and transport it (turn it over) to the next acceptor in the series. For Warburg's yellow enzyme, with dihydrocoenzyme I as the substrate and methylene blue as the next acceptor, the turnover number is fifty.

5. Hogness, T. R.: The Flavoproteins, in A Symposium on Respiratory Enzymes, Madison, Wis., University of Wisconsin Press, 1942, p. 136.

The prosthetic group of many of these enzymes, instead of being riboflavin phosphate, as in Warburg's yellow enzyme, is riboflavin-adenine-dinucleotide. The structural formula of this compound is shown in the accompanying figure.

To present a thorough explanation of the actions of each of these enzymes is beyond the scope of this paper. The reactions of two are represented in the following series:



Cytochrome C can be oxidized by oxygen in the presence of cytochrome C oxidase or by hydrogen peroxide in the presence of cytochrome C peroxidase. However, in the reduced form many of these riboflavin-containing compounds do not react readily with cytochrome C. In order to explain the transfer to the cytochrome series, it has been postulated [6] that possibly the succinate-fumarate system of Szent-Györgyi may be the link which connects the riboflavin enzymes with cytochrome C. Still another group of riboflavin enzymes are active in a series of reactions involving substrates other than hexose monophosphate. These substrates are levo and dextro amino acids, hypoxanthine, xanthine and certain aldehydes. These enzymes react directly with oxygen at a rapid rate, thereby differing from the previously mentioned group.

Although it may be seen from what has been said that the riboflavin-containing enzymes can take part in a great variety of oxidative reactions, it is not definitely established just how important these enzymes are to the organism. In fact, it has even been suggested that certain of them may "be looked upon as incinerators for disposing quickly of unwanted products." [7] Thus, it may be that an increased production of these "unwanted products" causes a relative insufficiency of riboflavin enzymes, which under normal conditions would be sufficient for their disposal. As an example of a condition in which a similar set of circumstances may exist, the appearance of ketone bodies in the urine in diabetes may be considered. Ketone bodies were once believed to represent the abnormal end products of fat metabolism in diabetes. The modern concept, however, is that, while their production is a normal process, in diabetes they are not disposed of rapidly enough and subsequently accumulate in the body and appear in the urine. It may be that the "unwanted products" disposed of by riboflavin enzymes are at times produced in amounts in excess of the body's normal supply of riboflavin

6. Ball, E.: Oxidative Mechanisms in Animal Tissues, in A Symposium on Respiratory Enzymes, Madison, Wis., University of Wisconsin Press, 1942, p. 22.

7. Ball,[6] p. 26.

enzymes for their disposal. Their subsequent accumulation may result in lesions, such as catarrhal ulcers and rosacea keratitis, which may be made to heal by supplying riboflavin enzymes in overabundance.

Thus, when one follows a molecule of riboflavin from its entrance into the body to its final position in cellular oxidation, one finds that it has to undergo numerous changes before it is capable of entering reactive processes. These include:

1. Phosphorylation, known to occur in the intestines [8] and possibly also performed in the cells of the liver or in other cells of the body.[9]

2. Combination with a protein, believed to take place within the cells, or combination with the remaining portion of the riboflavin-adenine-dinucleotide complex, which may take place in the liver, with subsequent combination with a protein. The properties of the final enzymes, even with identical prosthetic groups, are dependent on the proteins with which they are combined.

Even when these reactions occur normally, it is conceivable that a defect in the chain of oxidative reactions other than in the metabolism of the riboflavin-containing enzyme may be present. This defect may conceivably be in the reducing system (coenzyme I and II) or in the oxidizing system (cytochrome C, succinate-fumarate system, cytochrome oxidase or peroxidase). An increase in the amount of riboflavin enzyme such as might be brought about by giving riboflavin to a patient might, by the law of mass action, shift the reactions toward the right, even though the defect was in some other link in the chain.

With these considerations in mind, it is valid to inquire whether a patient who shows certain symptoms which are cured by the administration of riboflavin really can be considered as deficient in riboflavin. May the difficulty not lie, rather, in the series of reactions which convert free riboflavin into active enzymes or, on the other hand, in the series of reactions in which these enzymes participate? In the course of the past year we have carried out studies of cases of rosacea keratitis in an attempt to answer these questions. The data collected are presented herewith.

EXPERIMENTS AND RESULTS

Since it had been shown clinically that riboflavin will cure rosacea keratitis, it was hoped that studies of the urinary excretion of riboflavin in patients with this condition might disclose findings of aid to the clinician.

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8. Rudy, H.: Enzymatische Phosphorylierung des Lactoflavins, Naturwissenschaften **23**:286, 1936.

9. György, P.: Growth Promoting Activity of Lactoflavin Administered Orally and Parenterally, Proc. Soc. Exper. Biol. & Med. **35**:207 (Oct.) 1936.

Determinations of the urinary excretion of riboflavin had been made previously, biologic, microbiologic and fluorometric methods [10] being used. Axelrod and associates [10d] found no correlation between a test dose and the daily urinary excretion. Najjar and Holt,[10f] using a test dose of 1 mg. and a fluorometric method of assay, were able to demonstrate what they believed was a significant difference in urinary excretion of riboflavin in the first four hours between riboflavin-deficient patients and controls.

A review of the literature on the determination of riboflavin was made in 1938 by Ellinger,[11] who reached the conclusion that the biologic method, despite its drawbacks, is the most reliable. Fluorometric methods were considered unreliable, since oxidizing agents used to remove other fluorescent pigments from the urine destroy some of the riboflavin [12] and, also, the intensity of the fluorescence varies with the p_H and the salt concentration.[11] Since the biologic method is unsuited for the determination of riboflavin in blood and urine, we chose the microbiologic method of Snell and Strong.[13]

Our first approach to the problem lay in the study of the twenty-four hour excretion of riboflavin by patients with rosacea keratitis and by a series of normal controls selected from laboratory technicians and patients admitted to the hospital for conditions other than rosacea keratitis. Samples of urine were collected in large bottles, protected from the light so far as possible and stored in the refrigerator until assayed. An attempt was made to carry out all determinations as soon after collection as possible to minimize error from any possible destruction of riboflavin. The figures for the twenty-four hour urinary

10. (*a*) Emmerie, A.: Determination and Excretion of Flavins in Normal Human Urine, Nature, London **138**:164 (July 25) 1936. (*b*) Ferrebee, J. W.: The Urinary Excretion of Riboflavin, J. Clin. Investigation **19**:251 (Jan.) 1940. (*c*) Strong, F. M.; Feeney, R. E.; Moore, B., and Parsons, H.: The Riboflavin Content of Blood and Urine, J. Biol. Chem. **137**:363 (Jan.) 1941. (*d*) Axelrod, A. E.; Spies, T. D.; Elvehjem, C. A., and Axelrod, V.: A Study of Urinary Riboflavin Excretion in Man, J. Clin. Investigation **20**:229 (March) 1941. (*e*) Sebrell, W. H., Jr.; Butler, R. E.; Wooley, J. G., and Isbell, H.: Human Riboflavin Requirement Estimated by Urinary Excretion of Subjects on Controlled Intake, Pub. Health Rep. **56**:510 (March 14) 1941. (*f*) Najjar, V. A., and Holt, L. E., Jr.: A Riboflavin Excretion Test as a Measure of Riboflavin Deficiency in Man, Bull. Johns Hopkins Hosp. **69**:476 (Nov.) 1941. (*g*) Holt, A. E., Jr., and Najjar, V. A.: A Simple Method for Laboratory Diagnosis of Subclinical Deficiencies of Thiamin, Riboflavin and Nicotinic Acid, ibid. **70**:329 (March) 1942.

11. Ellinger, P.: Lyochromes in the Kidney, with a Note on the Quantitative Estimation of Lyochromes, Biochem. J. **32**:376 (Feb.) 1938.

12. Feeney, R. E., and Strong, F. M.: The Microbiological Determination of Riboflavin, J. Biol. Chem. **133**:xxxi (May) 1940.

13. Snell, E. E., and Strong, F. M.: A Microbiological Assay for Riboflavin, Indust. & Engin. Chem. **11**:346 (June) 1939.

excretion of riboflavin by the patient and control groups have been collected in table 1. It can be seen that the mean twenty-four hour excretion of riboflavin by the 16 patients was 618 micrograms and by the 14 controls was 1,032 micrograms. If the excretion of riboflavin is an index of the intake of this vitamin, it appears that the majority of patients with rosacea keratitis have an intake considerably below that of normal persons. On the other hand, there are patients with rosacea keratitis whose excretion of riboflavin is equivalent to that of normal persons. It is possible that in such patients the defect is not in the intake of riboflavin but in the metabolic cycle of riboflavin.

In carrying these studies further, we investigated the retention of a test dose of riboflavin by patients with rosacea keratitis and by normal

TABLE 1.—*Twenty-Four Hour Urinary Excretion of Riboflavin*

Patients with Rosacea Keratitis (16)		Normal Controls (14)	
Subject	Micrograms per 24 Hours	Subject	Micrograms per 24 Hours
B.	1,757	C.	729 (av.)
O.	360	E.	1,262 (av.)
H.	240	P.	1,401
Hu.	616	T.	1,394
M.	454	S.	867
G.	437	M.	842
P.	287	W.	1,123
Mc.	173	I.	1,875
W.	824	F.	1,156
Me.	1,846	Br.	682
Po.	1,161	Sm.	821
Br.	201	G.	1,141
Mo.	349	B.	747
T.	511	T.	407 (av.)
A.	132		
K.	546		
Mean	618	Mean	1,032

controls. In order to eliminate any variations resulting from differences in the ability to absorb riboflavin from the gastrointestinal tract, we administered all test doses parenterally. Several test doses were used. In the first series, the test dose was 1 mg. of synthetic riboflavin [14] administered intravenously. This dose suggested itself to us because it had been found so therapeutically efficacious in the treatment of rosacea keratitis. The results are collected in table 2. It can be seen from this table that there was little significant difference between the retention of the test dose by the patients with rosacea keratitis and the retention by the control group. The lack of difference may have been the result of variations in renal function, and, since the test dose was small, determination of its retention was probably subject to error due to daily variation in the riboflavin content of the diet.

14. Synthetic riboflavin was supplied by the S. M. A. Corporation.

The second test dose was 5 mg. of the sodium salt of riboflavin [15] dissolved in water and administered intramuscularly. This larger test dose administered intramuscularly was tried because previous studies [2d] had shown that a large percentage (20 per cent) of an intravenous dose is excreted within the first hour. It was felt that possibly this rapid

TABLE 2.—*Urinary Excretion of Riboflavin After Intravenous Injection of 1 Mg. of Riboflavin*

Patient	A Excretion in 24 Hours Preceding Injection, Micrograms	B Excretion in 24 Hours Following Injection, Micrograms	Retained (1,000 + A − B), Micrograms	Percentage Retained Retained (100) / 1,000
M.	454	1,532	0	0.0
H.	240	657	583	58.3
O.	360	1,302	58	5.8
Control				
E.	792	1,385	407	40.7
E′.	653	1,045	608	60.8
C.	842	1,814	27	2.7
T.	456	954	502	50.2

TABLE 3.—*Urinary Excretion of Riboflavin After Intramuscular Injection of 5 Mg. of Riboflavin in Water*

Patient	A Excretion in 24 Hours Preceding Injection, Micrograms	B Excretion in 24 Hours Following Injection, Micrograms	Retained (5,000 + A − B), Micrograms	Percentage Retained Retained (100) / 5,000
W.	824	1,334	4,490	89.8
Mc.	174	3,000	2,174	43.5
P.	287	2,347	2,940	58.8
G.	437	2,825	2,612	52.2
A.	132	2,980	2,152	40.4
K.	546	5,890	0	0.0
			Average	47.5
Control				
E.	731	5,706	0	0.0
E′.	870	4,676	1,194	23.9
C.	470	4,228	1,242	24.8
T.	440	3,576	1,874	37.5
			Average	21.5

excretion might be the result of a sudden increase in the blood riboflavin, which was passively spilled over into the urine. Intramuscular injections might allow a slower rise in the level in the blood and hence more time for the metabolism of the administered riboflavin. The results after this test dose have been collected in table 3. It can be seen that

15. The sodium salt of riboflavin was supplied by Winthrop Chemical Company, Inc., New York.

in all but 1 of the patients with rosacea keratitis the retention was higher than that of the controls. The average retention by the patients (47.5 per cent) was twice that by the controls (21.5 per cent).

Finally, in a further attempt to slow down the absorption of riboflavin, a 5 mg. test dose of riboflavin [15] suspended in sesame oil was administered intramuscularly. The results have been collected in table 4. In this series, too, it can be seen that the average retention was greater in the patients (43.0 per cent) than in the controls (30.8 per cent). In this series, too, individual discrepancies, which are discussed later, disturb the general picture.

TABLE 4.—*Urinary Excretion of Riboflavin After Intramuscular Injection of 5 Mg. of Riboflavin in Oil*

Patient	A Excretion in 24 Hours Preceding Injection, Micrograms	B Excretion in 24 Hours Following Injection, Micrograms	Retained (5 000 + A — B), Micrograms	Percentage Retained: Retained (100) / 5,000
Tu.	511	3,426	2,085	41.7
Mo.	349	1,592	3,757	75.1
Po.	1,161	4,154	2,007	40.1
Br.	201	2,673	2,528	50.6
M.	1,846	6,464	382	7.6
			Average	43.0
Control				
E.	1,817	5,863	954	19.1
E'.	727	4,464	1,263	25.3
C.	470	3,469	2,001	40.0
T.	440	3,507	1,933	38.7
			Average	30.8

COMMENT

At the beginning of this work, studies of the level of blood riboflavin in the patients and in the controls were undertaken, the modification of the Snell-Strong microbiologic method recommended by Eckardt, György and Johnson [16] being used. These studies were abandoned, however, when it was found that no significant difference could be demonstrated between the level in the patients and that in the controls. In both patients and controls, the level varied between 0.08 and 0.12 microgram per cubic centimeter. After the administration of riboflavin, no significant difference could be detected, even when samples of blood were drawn as soon as five minutes after the intravenous administration of 1 mg. of riboflavin.

16. Eckardt, R. E.; György, P., and Johnson, L. V.: Presence of a Factor in Blood Which Enhances the Bacterial-Growth Activity of Riboflavin, Proc. Soc. Exper. Biol. & Med. **46**:405 (March) 1941.

The determination of the twenty-four hour excretion of riboflavin as an index of riboflavin deficiency has certain drawbacks which make the interpretation of the results somewhat difficult. In the first place, the excretion of riboflavin in the urine follows closely the intake of this vitamin in the diet. This fact was well illustrated by a patient under our observation whose total urinary riboflavin was determined every hour throughout the day and night. Three definite peaks of riboflavin excretion occurred, each peak being reached shortly after the meal hour. This patient showed no signs of rosacea keratitis, but had been admitted to the hospital for other reasons. Furthermore, in determinations of the riboflavin excretion by one of our normal subjects on consecutive days, considerable variation from day to day was observed. When liver had been included in the diet, a pronounced increase in the excretion of riboflavin for that day was observed. This variation generally did not exceed 1,000 micrograms daily. In the second place, the excretion of riboflavin in the urine is dependent on the ability of the subject to absorb the riboflavin ingested from the diet. Finally, Najjar and Holt [10f] have shown that by placing a subject on a diet low in riboflavin it is possible to depress the urinary excretion of riboflavin to zero and maintain it there for some time with no evidence of symptoms developing.

With these precautions in mind, we do not feel that it is possible to determine the existence of riboflavin deficiency by a single determination of the twenty-four hour urinary excretion of riboflavin. Nonetheless, we do feel that the conclusion is warranted from our results that on the whole the intake of riboflavin by a series of patients with rosacea keratitis is considerably less than that of a control group selected from laboratory technicians and patients admitted to the hospital for reasons other than rosacea keratitis. This conclusion bears out our previous observation [2b] that the diet of most patients with rosacea keratitis is low in foodstuffs, such as milk, liver and eggs, which have a high riboflavin content.

From the data presented in this paper it is seen that the determination of the retention of a test dose of riboflavin may be used as a corollary in the determination of riboflavin deficiency in such patients. It must, however, be emphasized that the clinical diagnosis of rosacea keratitis is of primary importance; that is to say, no attempt has been made to diagnose rosacea keratitis on the basis of retention data. By the combined use of twenty-four hour excretion studies and retention studies, it is possible to differentiate between patients with a dietary deficiency and those who probably have an abnormality in the metabolism of riboflavin, including the enzymes themselves and the reactions in which they are active.

We found that 1 mg. administered intravenously is not a suitable test dose for retention studies. The reasons for this may be twofold:

First, the amount of riboflavin retained may be dependent on the state of renal function; second, this dose is so small that variations in the daily intake of riboflavin may mask its retention.

We have found that a test dose of 5 mg. dissolved in water and administered intramuscularly is the most satisfactory. Of 6 patients with rosacea keratitis studied by means of this dose, 5 could be considered as riboflavin deficient on the basis of a retention of 40 per cent or more. With a test dose of 5 mg. suspended in oil and administered intramuscularly, 3 out of 5 patients with rosacea keratitis could be considered as riboflavin deficient on the basis of a retention of 40 per cent or more. Of the 2 patients who could not be considered deficient on this basis, the retention of 1 was at the questionable level, as was that of 1 of the controls.

It is thus obvious that the majority of patients with rosacea keratitis show some degree of riboflavin deficiency on the basis of retention data. These patients range from those who are primarily riboflavin deficient to those who show little retention of riboflavin and who must be considered as suffering from a metabolic disorder which may be alleviated by massive doses of riboflavin.

One case has been unique among those of rosacea keratitis which have been under our observation:

The condition of a 28 year old white woman, seen on March 18, was diagnosed by slit lamp examination as rosacea keratitis of the left eye. The small marginal infiltrates were present at 2 o'clock. She was subjected to the usual regimen of treatment: 1 mg. of riboflavin was administered intravenously daily and 1 teaspoonful of the vitamin B complex preparation three times daily. Not only was there no relief of symptoms, but every four or five days a new marginal infiltrate appeared, above or below the initial lesions.

On April 21 the patient was admitted to the hospital for routine laboratory examination, which gave entirely negative results, with gastric achlorhydria absent.

On May 31 she was again admitted to the hospital. On June 1 she received 5 mg. of riboflavin intravenously, on June 3 a transfusion of 200 cc. of citrated blood, on June 5 a transfusion of 200 cc. of blood to which 5 mg. of riboflavin had been added immediately before transfusion and on June 7 a transfusion of 200 cc. of blood which had been incubated with 5 mg. of riboflavin at 0 C. for four days. The 600 cc. of blood was taken from one donor on June 3.

Clinical improvement was noticeable June 8, and within one week evidence of the previous infiltrates was absent.

After the injection of 5 mg. of riboflavin on June 1, the retention in twenty-four hours was calculated as 35 per cent. After the transfusion of blood plus riboflavin on June 5 and blood incubated with riboflavin on June 7, the retention was 58.4 per cent and 58 per cent, respectively. Clinically, improvement followed the transfusion of blood incubated with riboflavin, whereas transfusion of blood alone was followed by no clinical improvement. Thus it would seem that the transfused blood supplied some factor lacking in the patient, or initiated some process in the body, necessary for the utilization of riboflavin. Perhaps the blood helped to

phosphorylate the riboflavin by supplying enzymes in which the patient was lacking.

These data were compared with those obtained from another patient with rosacea keratitis who was submitted to the same regimen. This patient showed clinical improvement immediately after the first injection of 5 mg. of riboflavin alone, and the retention of riboflavin after the administration of riboflavin with blood was even less than the retention observed with the first 5 mg. dose administered alone. We feel that the observations on these patients warrant the conclusion that the former was suffering from a disturbance in riboflavin metabolism not affected by the continued administration of large amounts of riboflavin alone. The latter patient may be considered as suffering from dietary deficiency or abnormality correctable by riboflavin administered alone. Thus, we postulate that corneal disease may result from the existence of either one or both of two conditions, namely (1) dietary deficiency of riboflavin and (2) disturbance of the metabolism of riboflavin, either in its synthesis to active enzymes or in the chain of reactions in which these enzymes play an active role.

SUMMARY

1. Rosacea keratitis, marginal corneal ulcers and catarrhal corneal infiltrates have a common factor in their immediate response to the parenteral injection of riboflavin. These conditions are believed to result from an actual or relative insufficiency of the flavoprotein enzymes.

2. The average excretion and hence the intake of riboflavin by a series of patients with rosacea keratitis was found to be considerably less than those of a control group.

3. The intravenous injection of 1 mg. of riboflavin was not found to be a suitable test dose for retention studies. On the basis of the retention of a 5 mg. intramuscular test dose in water, 5 of 6 patients with rosacea keratitis could be considered as deficient. On the basis of the retention of a 5 mg. intramuscular test dose suspended in sesame oil, 3 of 5 patients with rosacea keratitis could be considered as deficient.

4. In our total experience, we have encountered only 1 patient with typical superficial vascularization and superficial marginal infiltrates in the arcus senilis area who has not responded satisfactorily to the intravenous use of riboflavin and the oral use of vitamin B complex. This patient's lesions did promptly heal when riboflavin and whole blood had been given. We feel that the whole blood supplied some factor or initiated some process necessary for the metabolism of riboflavin.

5. It is postulated that in addition to dietary deficiency, disorders in the metabolism of riboflavin enzymes may be responsible for the development of corneal disease.

Lakeside Hospital.

INITIAL AND RESIDUAL EFFECTS OF OPHTHALMIC PRISMS ON VISIBILITY AND ACCOMMODATION

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AND
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CLEVELAND

Recently there has been described a method of measuring the accommodative changes accompanying vergence without the variable of relative accommodation which is normally introduced by optical stimuli.[1] Since this characteristic is attained without inhibiting the neural coupling between vergence and accommodation,[2] the new technic appears unique for study of the effects of prismatic power on visibility and on accommodation. Thus, observed changes in these functions are assumed to be due to the ocular rotation induced by the addition of prismatic power. In the present discussion, these phenomena are considered from an experimental rather than from a clinical viewpoint.

The exploratory studies under consideration involved 2 adult nonpresbyopic subjects possessing emmetropic and orthophoric vision as determined by the usual methods of examination. In addition, their accommodation-convergence responses had been precisely measured by the sensitometric method of refraction.[1] Although the data relating visibility, accommodation and vergence may be typical of the normal person, they are here presented merely as detailed studies made under specific experimental conditions. Thus technics and trends are emphasized rather than quantitative values. Furthermore, it is recognized that the test periods during which the eyes were influenced by prismatic power were relatively short and that consequently the data are not necessarily indicative of ultimate physiologic responses.

TESTS AT 40 CM.

The data of chart 1 show the effects of base-in and base-out prisms on visibility and on the accommodative states of emmetropic eyes converged at a distance of 40 cm. In the experimental procedures, each

From the Lighting Research Laboratory, General Electric Company.

1. Luckiesh, M., and Moss, F. K.: New Method of Subjective Refraction Involving Identical Technics in Static and in Dynamic Tests, Arch. Ophth. **23:** 941 (May) 1940.

2. Luckiesh, M., and Moss, F. K.: Functions of Relative Accommodation, Am. J. Ophth. **24:** 423 (April) 1941.

prism was placed in the right aperture of a trial frame, which was worn throughout the test period, during which convex and concave lenses were placed successively in the Luckiesh-Moss sensitometer [1] in the process of refraction. This procedure permitted the subject to become somewhat habituated to the abducting or adducting prisms for a short time before the tests were begun, as well as during the time required to make six series of five measurements of visibility with each trial lens. Although it is not assumed that the adaptive responses to the addition of prismatic power were complete during the test periods, the symmetry of the relationships shown in chart 1 indicates that progressive changes in the accommodation-convergence coupling, if they occurred, were not

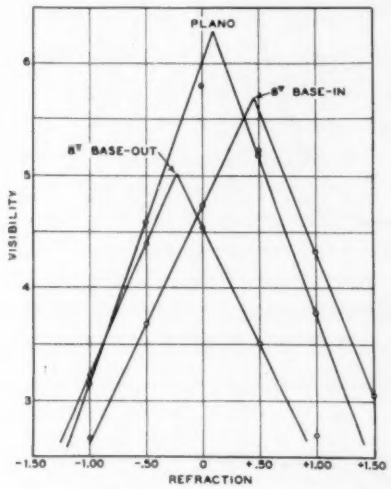

Chart 1.—Relations between visibility and refraction as measured with base-in and base-out prisms, respectively, before the right eye of an emmetropic subject. The fixation-distance was 40 cm. for all measurements.

Additional Spherical Power Required for Maximal Visibility When Prisms of 4 D. and 8 D., Respectively, Were Placed Base-in and Base-out Before the Right Eyes of Emmetropic Subjects

	Base-in		Base-out	
	8 D.	4 D.	4 D.	8 D.
Subject A	+ 0.36	+ 0.13	— 0.24	— 0.33
Subject B	+ 0.46	+ 0.20	— 0.10	— 0.20
Average	+ 0.42	+ 0.16	— 0.18	— 0.26

sufficient to distort seriously the visibility-refraction relationships. Corresponding data for subject B are presented in the accompanying table.

The data of the table were derived from graphs similar to those of chart 1. In all a total of seven hundred and fifty measurements of

the visibility of the sensitometric test object were made by each of the 2 subjects on five different days. The five sets of data were reasonably concordant with respect to the accommodative changes induced by the respective addition of base-in and base-out prisms of 8 D. In a consideration of chart 1, it should be recognized that straight lines were drawn through the plotted points merely as a geometric expedient for determining the additional dioptric power which yielded maximal visibility in each case. The detailed relationships between visibility and

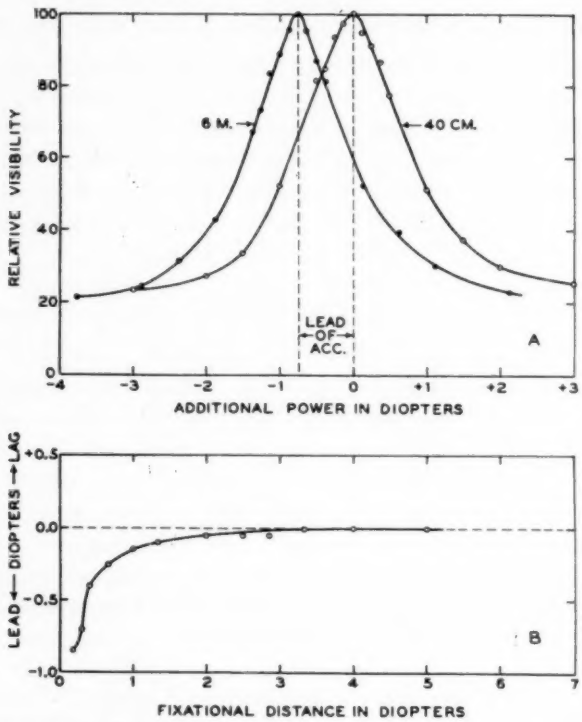

Chart 2.—Data for a typical adult emmetropic subject. *A*, relations between visibility and refraction for fixation distances of 6 meters and 40 cm. The curves were plotted from average results obtained on eight different occasions; to facilitate comparison, the visibility data were plotted on a percentage basis. *B*, relation between accommodation and convergence determined from two concordant examinations. The data are for the right eye, with accurately controlled convergence.

refraction for fixation distances of 6 meters and 40 cm., respectively, are shown for the same subject in chart 2. These data established the fact that the experimental procedures per se do not prevent changes in

accommodation due to ocular rotation while preventing relative accommodation to optical stimuli.

The visibility-refraction graphs of chart 1 show that the addition of either base-in or base-out prismatic power decreases visibility even though the ametropia introduced by the prisms is presumably corrected by appropriate lenses. Similar graphs were obtained for subject B. Thus it appears that the effects of prismatic power extend beyond simple changes in focus. It is conceivable, for example, that an aniseikonic condition is created by the monocular addition of prismatic power which produces dissimilar optical paths. No significance is attached to the fact that a slightly higher visibility was obtained with base-out power, since a small but opposite effect was indicated by subject B.

It will be noted that additional plus power is required for maximal visibility when the test object is viewed through base-in prisms. Similarly, additional minus power is required with base-out prisms. The directions of these refractive changes are consistent with those expected on theoretic grounds in the case of emmetropic eyes fixated at the test distance of 40 cm. For subject A, it appears that an accommodative change of about 0.36 D. accompanied the monocular addition of 8 D. of prismatic power. This is about one half of the usual phoria correction. Similar relationships between accommodation and vergence were obtained for subject B. It will be noted that the phoria corrections indicated in chart 1 are based directly on the refractive condition which actually yielded maximal visibility when the eyes were converged at a point in the plane of the test object.

A comparative analysis of charts 1 and *2B* indicates that an inward rotation of the eyes resulting from (1) a nearer fixation and (2) an addition of base-out prismatic power with constant fixation produces dissimilar accommodative effects. For example, the data of chart 1 reveal a definite shift in accommodation induced by prismatic power, whereas an equal degree of ocular rotation resulting from a nearer fixation (chart *2B*) did not produce a detectable change in relative accommodation. These differential reactions suggest the participation of influences not mechanically associated with ocular rotation. It is possible, for example, that the maintenance of conjugacy in near vision is facilitated by an "awareness" of the position of the object in space. Presumably, this factor would be most influential in situations involving an actual shift in fixation as well as ocular rotation.

A second investigation of near vision involving subject A likewise revealed that the addition of any prismatic power definitely decreased visibility, as will be noted from chart 3. In this experiment, various prisms from 8 D. base out to 8 D. base in were successively placed

before the right eye and the visibility of the standard test object[1] measured for each condition. The measurements began with an 8 D. base-out prism and progressed to an 8 D. base-in prism, and in alternate tests the order of presenting the series of prisms was reversed. A plano lens was used for the condition of zero prismatic power. The relationships of chart 3 involved a total of four hundred and twenty measurements of visibility made on six occasions. In general the individual sets of data from which chart 3 was derived were much more erratic than those for chart 1. This is statistical evidence of the presence of uncontrolled variables in the second experiment.

It will be noted that a lower degree of visibility is obtained with base-out prisms when the latter are presented in order of increasing power rather than in the reverse order. This indication of hysteresis or residual effects is pronounced in the case of distant vision, as will be noted from chart 4. The data of chart 3 also indicate that the

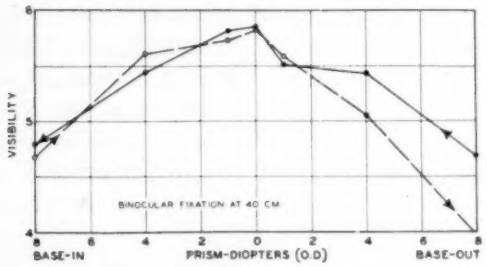

Chart 3.—Relations between visibility and vergence for an emmetropic subject with fixation at 40 cm.

reduction in visibility due to base-in prisms is practically independent of the order of presenting the prisms. However, this is not the case with base-out prisms.

TESTS AT 6 METERS

Some effects of prismatic power on visibility for a fixation distance of 6 meters are shown for subject A in chart 4. These data were obtained by successively placing the various prisms in the sensitometer and measuring the visibility of the standard test object under each condition. Thus, the subject had little opportunity to become adapted to a given prism except as such adaptation may have taken place during the series of five measurements of visibility made with each prism. In this respect, the experimental conditions were similar to those prevailing in the second near vision test. However, in both investigations, a given prism was before the right eye only a few minutes. The binocular measurements began with an 8 D. base-out prism and progressed to a 5 D. base-in prism, and in alternate tests, the order of presenting the

prisms was reversed. The relationships of chart 4 involve a total of one thousand and eighty measurements of visibility made on twelve occasions. These separate tests consistently revealed the same trends.

A salient characteristic of these data is the marked influence on visibility of the order of presenting the prisms. In general, the locus of visibility may be described as a hysteresis loop, with the qualification that the two branches of the so-called loop were determined on different occasions. In recognition of this fact, the sections *AE* and *CD* of the loop are represented by broken lines. The boundary *AE* is entirely arbitrary, whereas the boundary *CD* corresponds to a degree of abduction just short of that which would produce diplopia. Obviously, the disparity between the two curves of chart 4 cannot be explained simply on a basis of geometric optics.

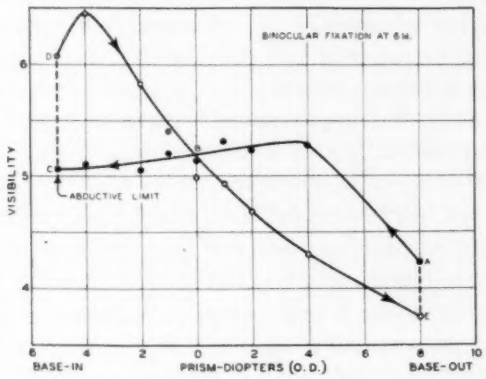

Chart 4.—Relations between visibility and vergence for an emmetropic subject with fixation at 6 meters.

It will be noted that the base-in to base-out branch *DBE* of the loop bears little resemblance to the base-out to base-in branch *ABC*, either in form or in the degree of visibility reached. However, a difference between the two visual situations represented in chart 4 would be expected from clinical tests. Obviously the sharp monotonic decrease in visibility of the section *BE* permitted "base-out to blur" measurements, whereas corresponding "base-in to blur" data were not obtained, since visibility remained practically constant until diplopia occurred.

In this case, the highest degree of visibility was obtained with the monocular addition of a 4 D. base-in prism when the addition was made in the base-in to base-out order. Since abduction decreases the refractive power of the eye, the attainment of maximal visibility at distance with base-in power is consistent with the theory that the so-called emmetropic eye is myopic at distance to the extent of about

0.75 D. when relative accommodation is avoided.[1] For subject A, it appears that maximal visibility could be achieved with either a 4 D. base-in prism added initially or a 0.75 D. concave lens. However, the same amount of base-in power only slightly altered visibility when it was gradually added.

It will also be noted from chart 4 that the initial addition of 8 D. of base-out power resulted in a higher degree of visibility (*A*) than was obtained when the same amount of base-out power was gradually added (*B* to *E*). From a graphic viewpoint, it appears that the curve *ABC* has been shifted about 4 D. in the direction of base-out power with respect to the curve *BDE*. Assuming that the normal eye is myopic at distance, in the absence of adequate optical stimuli for accommodation, it is conceivable that the anomalous ocular movements of adduction, in distant vision, would serve as stimuli for negative relative accommodation. This function appears to be capable in the so-called normal person of supplying about 0.75 D. of negative power.[2] Obviously, visibility would be increased if this function became operative. It will be noted from chart 4 that a straight line projection from *A* through the 4 D. point indicates that approximately maximal visibility would be obtained without prismatic power if the conditions prevailing at *A* were maintained. This analysis supports the theory that the higher visibility at *A* was due to the functioning negative relative accommodation.

As the amount of base-out power is progressively reduced (curve *ABC*), with a concomitant reduction of the induced hyperopia, visibility is further increased, as would be expected. At the same time, however, the stimulus for negative accommodation may also be decreased. Hence an optimum in visibility is indicated on theoretic grounds. If the higher visibility at *A* depends on negative relative accommodation, it seems reasonable to assume that this function is not operative at *B*.

The extended plateau of optimum but subnormal visibility of the curve *ABC* in chart 4 is suggestive of the typical plateau of visual acuity obtained with concave lenses when the accommodation is actively in play. Obviously, sufficient negative power to produce maximal visibility is not supplied through progressive increases in abduction notwithstanding the fact that this function is capable of supplying negative power when added initially. It is possible that a progressive increase in abduction may be an adequate stimulus for positive relative accommodation and that the latter inhibits the reflex addition of negative power as a result of outward ocular rotation.

These considerations suggest that the so-called hysteresis effects indicated in charts 3 and 4 arise from the variable functioning of relative accommodation when prismatic power is added in different ways.

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MARGINAL DEGENERATION OF CORNEA

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As marginal degeneration of the cornea is not rare but is being overlooked because of its mildness, it seems timely to report a case.

First described by Trümpy [1] in 1881 as a peculiar deformity of the cornea, it has been given a variety of names, such as peripheral furrow keratitis, by Schmidt-Rimpler,[2] in 1889; ectatic marginal dystrophy, in 1900; peripheral sclerosis and atrophy, by Fuchs,[3] in 1901; peripheral corneal ectasis, by Lauber,[4] in 1905, and senile marginal atrophy, by Fuchs, in 1915.[4a]

REPORT OF A CASE

A white man aged 21 presented himself at the Research and Educational Hospitals, University of Illinois, complaining of recurring attacks of irritation and slight photophobia of the right eye for the past year and similar attacks in the left eye during the previous month. Each attack lasted a few days.

History.—The history did not reveal anything relevant. The patient had three brothers, living and well. There was no family history of ocular abnormalities.

Ocular Examination.—The ocular movements were normal in all directions. Examination of the right eye disclosed that the upper lid drooped a little, with slight narrowing of the palpebral fissure, and that the palpebral conjunctiva was injected. The bulbar conjunctiva became congested on slight manipulation. There was slight pericorneal congestion. The cornea showed a circular opacity near the limbus varying in width from 3 mm. vertically to 1.5 mm. horizontally (fig. 1,*a*). A pannus covered the entire opacity, and its loops ended abruptly at the inner margin. Within the opacity there were many white, chalky, punctate opacities. The left eye had a semilunar vascularized opacity, about 1.5 mm. in width, from 10 to 2 o'clock.

Slit lamp examination showed a whitish gray opacity of the anterior part of the right cornea, with chalky punctate opacities. The distribution of the finer vessels stopped abruptly at the gray line and covered the entire ring. The posterior surface of each cornea showed some irregularity of curvature at the site

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From the Ophthalmology Department of the University of Illinois College of Medicine.

1. Trümpy, D.: Zwei Fälle einer eigenthümlichen Hornhautdeformität, Zurich, G. Fussli u. Co., 1881.

2. Schmidt-Rimpler, H.: Augenheilkunde und Ophthalmoskopie, ed. 4, Berlin, F. Wreden, 1889, p. 486.

3. Fuchs, E.: Arch. f. Ophth. **52**:317, 1901.

4. Lauber, H.: Klin. Monatsbl. f. Augenh. **43**:382, 1905; cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1996.

4a. Fuchs, E.: Arch. f. Ophth. **59**:386, 1915.

of the groove. This was more marked in the right eye and evidently represented the beginning of localized ectasia. The anterior chambers were normal and the irises brown, and the pupils reacted to light and in accommodation.

Without correction the vision of the right eye was 0.4 and that of the left 0.6 — 2. With a correction of — 0.50 D. sph. ⌒ — 0.50 D. cyl., axis 150, the vision of the right eye was 0.8. With a correction of — 0.50 D. sph. ⌒ + 0.50 D. cyl., axis 75, that of the left eye was also 0.8.

The Wassermann reaction of the blood was negative, as was the reaction to the Mantoux test. The basal metabolic rate was + 3. The differential blood count was normal. A culture of material taken from the conjunctiva was negative. No inclusion bodies or eosinophils were found in smears.

Treatment.—One-third grain (0.02 Gm.) of sulfanilamide per pound of body weight was given daily for four days. One-fourth grain (0.015 Gm.) was given

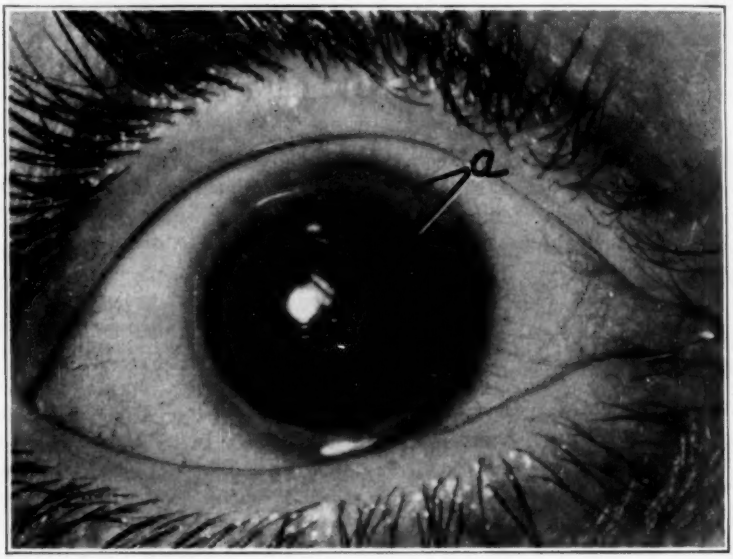

Fig. 1.—The right eye, showing a circular corneal opacity (*a*) near the limbus.

daily for the following six days. Five per cent sulfathiozol (2-[paraaminobenzenesulfonamido]-thiazole) ointment was used at bedtime. Large doses of vitamins A, B and D were administered, two ampules each containing 50 mg. of thiamine hydrochloride being given twice a week by injection. Glasses were prescribed, soft-lite no. 2. With the vitamin treatment and use of the soft-lite glasses, the patient showed improvement, and the photophobia disappeared. The patient was warned about possible effects resulting from pressure against his eyes.

COMMENT

The cause of the disease is unknown.

About 559[5] cases have been described in some detail in the literature. Seventy-five per cent of the patients were male. Their ages

5. Gifford, S. R.: Am. J. Ophth. **8**:16, 1925.

varied between 10 and 70 years, one third of the total being under 40. The disease was usually bilateral, but not always in the same stage of development in the two eyes.

Clinical Course.—Clinically, the disease starts with a peripheral opacity of a fine punctate constitution closely resembling an arcus senilis and leaving the same clear zone between itself and the sclera except in the deepest layers of the stroma, which are vascularized; it usually commences superimposed on an arcus senilis, but it may occur in the absence of this lesion. Gradually a gutter-like furrow appears, usually between the arcus and the limbus but occasionally central to it. The epithelium remains intact, and as the gutter deepens its peripheral side shelves gradually but the central wall rises sharply and perpendicularly, the sharp edge standing out as a white line. The floor of the gutter is vascularized by radial vessels from the limbus, which trespass a little way beyond the furrow. The furrow deepens; the floor gets progressively thinner and eventually gives way before the intraocular pressure and begins to bulge, forming an ectasia. Finally, rupture may occur, involving a perforation with a prolapse of the iris.

The process is extremely slow, and the development of ectasia may take ten to twenty years. The upper part of the cornea is usually affected first, and the condition develops there most rapidly; the furrow slowly spreads circumferentially, but ectasia in the lower part is extremely rare. The usual picture is that of an ectasia above and a furrow below or of localized vesicular ectasias along the course of a furrow. The sensitivity of the cornea is unimpaired centrally; it is diminished in the floor of a furrow and absent in an ectatic area.

Subjective Symptoms.—The essential symptom is slowly progressive visual deterioration due to the development of astigmatism brought about by flattening of the cornea in the meridian which passes through a furrow or ectasia. Some patients show an intermittent symptom of irritation resembling a mild conjunctivitis. The symptoms are frequently so little in evidence that the patient may be unaware that a diseased condition exists.

The myopic astigmatism present in nearly all cases may reach an extreme degree. It reached 21 D. in Marquézy's [6] case and 22 D. in Ischreyt's [7] case, and it often reaches 16 to 18 D., as in Gifford's [5] second case. While it progresses up to a certain point the increase often stops, leaving refraction about the same for years.

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6. Marquézy, R.: Contribution à l'étude clinique, biologique, étiologique et expérimentale de la sclérose en plaques, Thesis, Paris, no. 217, 1924; Ann. d'ocul. **162**:157, 1925.

7. Ischreyt, G.: Klin. Monatsbl. f. Augenh. **45**:197, 1907.

Differential Diagnosis.—Some observers have considered the condition simply a senile change related to arcus senilis (Fuchs; Gilbert [8]). This view cannot now be held, because a fair number of cases in young persons are on record, as pointed out by Gonzalez.[9] The condition probably began in his case at 16 and in Marquézy's [6] case at 10 years of age. Gifford's 4 patients were under 36, with no signs of arcus.

In many reported cases it is likely that the condition was of long standing when it first was seen. Fuchs [3] recognized this form of degeneration as occurring rarely in young persons but thought, on account of its common location on the upper margin, where the gerontoxon commonly develops first, that, if not actually a result of arcus senilis, it represented a degenerative process analogous to it. Handman [10] has even suggested that the flattening of the vertical meridian which is so frequent in old age represents a tendency toward the same form of degeneration or weakening of the upper portion of the cornea. In any case, the upper margin would seem to be a place of least resistance in the cornea, its weakness making it easily susceptible to both marginal dystrophy and gerontoxon, even though these may be entirely different conditions. There can be no doubt that the condition under discussion is degenerative in origin, the inflammatory symptoms observed in about half the cases being secondary and possibly due to a cellular necrosis in the cornea. In line with its dystrophic nature is the usual involvement of both eyes.

Pathologic Picture (fig. 2).—In 1 case Fuchs enucleated the eye after glaucoma developed and was able to report the following pathologic changes, in the order given:

1. Destruction of Bowman's membrane.

2. A chemical change of unknown character in the cement substance of the corneal lamellas, causing a disorganization of the lamellas, which become loosened.

3. Destruction of a small part of the corneal lamellas, resulting in a thinning of the cornea.

Prognosis.—The prognosis is good. The process is extremely slow, and the development of ectasia may take ten to twenty years.

Among the complications of the condition is rupture of the cornea, spontaneous or due to slight trauma. Uhthoff's [11] patient, a man of 59, had noted attacks of inflammation in each eye for ten years. His first visit to Uhthoff was after he had struck his right eye with his

8. Gilbert, W.: Klin. Monatsbl. f. Augenh. **46**:145, 1908.
9. Gonzalez, J. de J.: Am. J. Ophth. **7**:452, 1924.
10. Handman, M.: Klin. Monatsbl. f. Augenh. **72**:11, 1924.
11. Uhthoff, W.: Klin. Monatsbl. f. Augenh. **68**:289, 1922.

little finger, producing a rupture at the thinned upper margin, through which the lens escaped. Typical marginal dystrophy, with formation of a groove, was seen in other parts of the cornea and in the other eye. Twelve years later he came in with an exactly similar condition of the left eye, which he had struck with his thumb while washing. He was left with vision of counting of fingers in each eye. Uhthoff has seen another patient with perforation and prolapse of the iris. A second possible complication is secondary infection of the thinned area. In one of Axenfeld's [12] cases a typical Mooren ulcer developed at the site

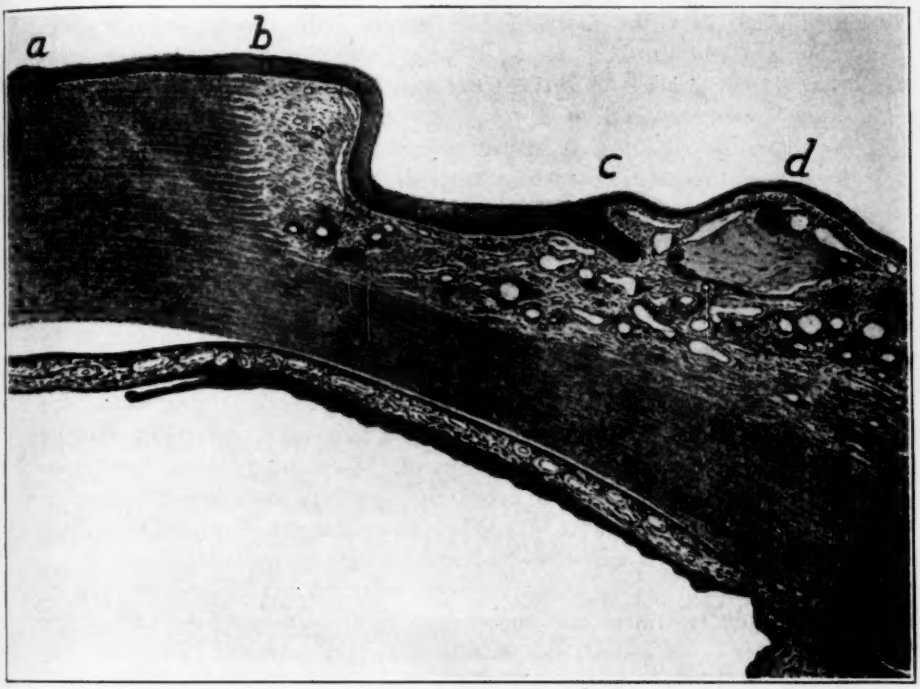

Fig. 2.—Pathologic picture of marginal degeneration of the cornea (from Fuchs [3]): *a*, end of Bowman's membrane, which is replaced by loose connective tissue; *b*, the changing of the large area of loose connective tissue, characteristic of the floor of the gutter; *c*, bud of epithelial layer penetrating into the loose connective tissue; *d*, the limbus.

of an old marginal dystrophy in each eye, resulting in an opacity involving the whole right cornea and the upper half of the left cornea. In a second case Axenfeld was obliged to operate for cataract on a woman with bilateral marginal dystrophy with ectasia. The borders of the operative wound became infiltrated, and a ring ulcer developed. This

12. Axenfeld, T.: Klin. Monatsbl. f. Augenh. **45**:578, 1907.

healed, however, leaving vision of 6/12. He stated the belief that this process in his second case was a form of necrosis due to poor nutrition and that the case is evidence that faulty nutrition is a cause of marginal dystrophy.

In one of Rupprecht's [13] cases a serpent ulcer developed and the eye was enucleated. In another case sections showed complete absence of Bowman's membrane and almost complete absence of corneal lamellas in the ectatic portion. The process had involved the whole thickness of the cornea, and aqueous had been forced through the resulting connective tissue, forming a cyst. The complete absence of Bowman's membrane over the diseased area agrees with the findings in Seefelder's [14] and Fuchs's [3] cases, in which also the eye came to enucleation. Degeneration of the corneal lamellas was also present in these cases, extending entirely through the cornea in Seefelder's case but involving only the superficial half in Fuchs's case, the loss being replaced by granulation tissue, which in Seefelder's case contained numerous fat globules. The portion of the cornea excised by Fisher [15] and examined by Coats [16] showed a most unusual thickening of Descemet's membrane, five or six layers being distinguishable, which gave it a total thickness of 55 microns in one place. This thickening was evidently formed by successive deposits to cover numerous cracks which were seen to be present in older layers.

Treatment.—The literature shows that Terrien [17] in 1900 and Adamantiadis [18] in 1910 cauterized an ectatic area repeatedly, thereby reducing the astigmatism. Excision of the ectatic portion, with reenforcing of the wound with a conjunctival flap, has been effective on several occasions (Lauber [4]). When an ectatic area becomes thin great care must be taken to avoid accidental rupture by trauma.

The patient whose case has been reported has responded well to the vitamin treatment and the change of glasses, with use of soft-lite lenses. It is, of course, too soon to predict the results and claim that this is the proper method of treatment.

25 East Washington Street.

13. Rupprecht, J.: Klin. Monatsbl. f. Augenh. **45**:34, 1907.
14. Seefelder: Klin. Monatsbl. f. Augenh. **44**:61, 1906.
15. Fisher, J. H.: Tr. Ophth. Soc. U. Kingdom **30**:25, 1910.
16. Coats, G.: Tr. Ophth. Soc. U. Kingdom **31**:5, 1911.
17. Terrien, F.: Arch. d'opht. **20**:12, 1900; **39**:523, 1921; cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.
18. Adamantiadis, B.: Arch. d'opht. **30**:46, 1910; cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

A COMPARISON OF OCULAR IMAGERY

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The work which in recent years has been developed at the Dartmouth Eye Institute, Hanover, N. H., by Ames and his associates [1] has become familiar to most ophthalmologists. The practical clinical application of the correction of aniseikonia has apparently not been demonstrated sufficiently to establish in the minds of practicing physicians the need for considering the condition a part of the symptom complex of asthenopia. The reaction of many physicians and laymen has been that there has been considerable publicity without a commensurate guarantee of symptomatic relief.

This paper consists of a comparison of two instruments designed for the purpose of measuring the relative discrepancy in size and shape between the ocular images of the two eyes. The first instrument is the "eikonometer," designed by the Dartmouth Eye Institute [2] in conjunction with the American Optical Company. The other is the "comparator," [3] designed by Kerry and his co-workers at Belgard-Spero, Inc., Chicago. This instrument is based on the principle of persistence of retinal images for short intervals after the exciting objects have been removed from view, i. e., the same principle as that of the motion picture projector. Briefly, it consists of two synchronized projectors with shutters rotating in front of the eyes. The projected target as seen by one eye is fixed; the other is variable in size and position. The one projection observation is movable, so as to compensate for heterophorias which may exist. The size difference is read on a vernier.

Twenty-five students of Northwestern University Medical School were used in this study. They were selected without regard to refractive errors. The only requirement was that they must have at least

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From the Department of Ophthalmology, Northwestern University Medical School.

1. Ames, A., Jr.; Gliddon, G. H., and Ogle, K. N.: Size and Shape of Ocular Images, Arch. Ophth. **7**:576-597 (April) 1932. Carleton, E. H., and Madigan, L. F.: Size and Shape of Ocular Images, ibid. **7**:720-738 (May) 1932. Ames, A., Jr., and Ogle, K. N.: Size and Shape of Ocular Images, ibid. **7**:904-924 (June) 1932.

2. Ames, A., Jr., and Gliddon, G. H.: Ocular Measurements, Tr. Sect. Ophth., A. M. A., 1928, pp. 102-175. Ames, A., Jr.; Ogle, K. N., and Gliddon, J. H.: Corresponding Retinal Points, the Horopter and Size and Shape of Ocular Images, J. Optic. Soc. America **22**:538 (Oct.); 575 (Nov.) 1932.

3. Patents pending at the United States Patent Office.

Comparison of Measurements Taken with the Comparator and the Eikonometer

Case No.	Name	Comparator: Magnification in Left Eye * Axis 180	Comparator: Magnification in Left Eye * Axis 90	Comparator: Magnification in Right Eye * Axis 180	Comparator: Magnification in Right Eye * Axis 90	Comparator: Heterophoria	Eikonometer: Magnification in Left Eye * Axis 180	Eikonometer: Magnification in Left Eye * Axis 90	Eikonometer: Magnification in Right Eye * Axis 180	Eikonometer: Magnification in Right Eye * Axis 90	Eikonometer: Heterophoria
1	R. A.	3.8% +2.9% −11.0%	0.0% +1.0% −0.0%	.....	.....	Esophoria 0.5 △	No size difference in either eye +0.5% −0.5%	 +1.0% −0.75%	 +0.5% −0.5%	 +1.0% −1.0%	No deviation
2	W. A.	.....	.....	1.2% +1.2% −8.2%	0.4% +4.2% −2.6%	Right hyperphoria 2.0 △ Exophoria 0.5 △	.....	.....	0.0% +0.5% −0.5%	1.75% +1.0% −0.5%	No vertical deviation Exophoria 9.0 △
3	O. B. D.	0.5% +1.7% −5.1%	0.75% +0.4% −5.0%	.....	.....	Right hyperphoria 0.1 △ Exophoria 0.4 △	0.25% +0.5% −0.5%	0.75% +0.5% −0.5%	.....	.....	Right hyperphoria 0.5 △ No horizontal deviation
4	C. B.	0.8% +2.5% −6.6%	.....	.....	4.4% +3.7% −1.4%	Left hyperphoria 1.6 △ Esophoria 3.0 △	1.5% +0.25% −0.25%	.....	.....	3.5% +0.25% −0.25%	Right hyperphoria 2.5 △ Esophoria 2.0 △
5	J. C.	2.1% +1.6% −7.6%	4.9% +6.4% −4.9%	.....	.....	Right hyperphoria 0.8 △ Exophoria 0.25 △	0.75% +0.25% −0.25%	1.0% +0.5% −0.5%	.....	.....	Left hyperphoria 0.25 △ Exophoria 1.0 △
6	I. C.	1.0% +8.9% −3.2%	1.9% +1.4% −5.3%	.....	.....	No deviation	No size +0.5% −0.5%	 +0.5% −0.5%			Exophoria 1.0 △
7	L. C.	.....	2.2% +11.1% −9.3%	4.3% +5.5% −6.5%	.....	Right hyperphoria 0.7 △ Exophoria 4.5 △	.....	0.75% +1.0% −0.75%	2.0% +0.5% −0.5%	.....	No vertical deviation Exophoria 5.0 △
8	A. C.	2.4% +3.1% −13.0%	0.0% +4.4% −1.1%	.....	.....	Right hyperphoria 1.1 △ Esophoria 1.5 △	.....	2.75% +0.5% −0.5%	0.5% +0.5% −0.5%	....	No deviation
9	H. C.	.....	.....	0.1% +5.7% −8.9%	0.3% +6.8% −5.8%	Right hyperphoria 1.0 △ Exophoria 0.8 △	0.5% +0.25% −0.25%	0.5% +1.0% −1.0%	.....	.....	No deviation
10	W. F.	2.7% +6.1% −6.1%	0.5% +1.0% −6.3%	.....	.....	Right hyperphoria 0.7 △ Esophoria 1.3 △	.....	.....	0.0% +1.0% −1.0%	2.5% +1.0% −1.0%	No deviation
11	R. F.	0.8% +2.0% −6.7%	.....	.....	0.4% +3.1% −3.8%	Right hyperphoria 0.6 △ Esophoria 0.1 △	.....	.....	0.0% +0.5% −0.5%	0.5% +0.5% −0.5%	No deviation
12	H. F.	1.3% +4.2% −5.9%	4.7% +3.0% −8.1%	.....	.....	Exophoria 0.3 △	0.25% +0.5% −0.5%	0.25% +0.5% −0.5%	.....	.....	No deviation
						Left hyperphoria 0.4 △	.....	.....	4.0%	0.0%	No deviation

13	E. G.	.....	.....	1.1% +7.6% −13.9%	1.5% +10.7% −5.9%	Left hyperphoria 0.4 △ Exophoria 1.9 △	.....	.....	4.0% +1.0% −1.0%	0.0% +2.0% −3.0%	No deviation
14	D. H.	0.0% +1.1% −4.6%	0.2% +3.1% −3.6%	.....	.....	Right hyperphoria 0.6 △ Esophoria 2.4 △	0.5% +0.25% −0.25%	.....	.....	0.25% +0.25% −0.25%	No deviation
15	H. H. D.	2.8% +0.1% −8.8%	2.0% +3.4% −4.2%	.....	.....	Left hyperphoria 1.3 △ Esophoria 3.6 △	+0.5% −0.5%	No size +0.5% −0.5%			No deviatian
16	V. H.	0.8% +3.9% −2.0%	2.3% +2.4% −7.2%	.....	.....	Right hyperphoria 0.2 △ Exophoria 0.2 △	0.0% +1.0% −1.0%	2.5% +2.0% −2.0%	.....	.....	No deviation
17	H. H.	1.2% +3.1% −5.7%	.....	.....	1.0% +3.5% −2.1%	Right hyperphoria 0.4 △ Esophoria 1 4 △	0.5% +0.5% −0.5%	.....	.....	1.0% −0.75% −0.75%	No deviation
18	R. H.	4.0% +6.0% −7.4%	0.3% +3.0% −2.5%	.....	.....	Right hyperphoria 0.7 △ Esophoria 0.1 △	0.25% +0.25% −0.25%	0.25% +0.25% −0.25%	.....	.....	No deviation
19	C. J.	.....	2.3% +1.7% −4.0%	1.4% +6.0% −3.1%	.....	Right hyperphoria 0.3 △ Exophoria 2.4 △	0.0% +0.25% −0.25%	0.5% +0.25% −0.25%	.....	.....	Exophoria 4.0 △
20	L. L.	.....	6.5% +2.0% −0.1%	3.9% +20.1% −6.0%	.....	No deviation	.....	1.0% +1.0% −1.0%	2.5% +1.0% −1.0..	.....	No deviation
21	G. L.	.....	0.7% +9.1% −11.6%	0.9% +13.6% −5.1%	.....	Right hyperphoria 1.9 △ Esophoria 1.6 △	.....	0.75% +1.0% −1.0%	1.0% +2.5% −2.5%	.....	Right hyperphoria 2.0 △
22	I. M.	.....	.....	0.3% +3.2% −1.4%	0.2% +3.3% −3.5%	Right hyperphoria 2.7 △ Esophoria 0.4 △		No size difference	+1.0% −1.0%	+0.75% −0.75%	Right hyperphoria 1.0 △
23	M. N.	2.7% +1.8% −13.7%	2.6% +0.7% −16.3%	.....	.....	Right hyperphoria 0.7 △ Exophoria 0.9 △	0.5% +0.5% −0.5%	0.5% +0.5% −0.5%	.....	.....	Exophoria 3.0 △
24	J. R.	.....	2.1% +5.3% −6.3%	2.2% +7.2% −7.3%	.....	Right hyperphoria 1.8 △ Exophoria 1.6 △	.....	2.5% +0.5% −0.5%	0.0% +0.5% −0.5%	.....	Exophoria 3.0 △
25	M. W.	2.7% +1.5% −0.6%	0.7% +1.4% −0.1%	.....	.....	Right hyperphoria 0.3 △ Exophoria 0.1 △	+0.5% −0.5%	No size difference +1.0% −1.0%			No deviation

* The plus and the minus figure in each case represent the percentage of magnification which must be added to or subtracted from the prescription for the patient to recognize the change on the target.

20/20 vision in each eye. If they required glasses to obtain this, they were measured with the same lenses with each instrument; either their own glasses or lenses from a Tillyer trial set were used. Some of the subjects had vague asthenopic symptoms; others had none. Those with pronounced heterophoria (as measured with the Maddox rod), squint or ophthalmic disease were excluded. All of the subjects were in the second or the third decade.

Clinicians who have worked with aniseikonia are well aware of a phenomenon known as sensitivity, or limitation of discernment of size differences. A person will manifest a tolerance for certain size differences, as shown by the size readings on the instrument, which he will not notice. These limits of tolerance may well have some bearing on the relief of asthenopic symptoms. The sensitivity of the subject to relative size differences is recorded as the plus and minus percentage necessary for him to realize that the setting has been changed. The close relationship between the direction of the phoria and the meridian of greatest tolerance was apparent in most of the cases studied.

Measurements were taken in two principal meridians: the horizontal and the vertical. In the results as recorded in the table, the eye in which magnification occurred is stated. To correct for this, size must be added to the opposite eye. The meridians are recorded as in the correction of astigmatism with ordinary power lenses; i. e., axis 180 means size in the vertical meridian and axis 90 that in the horizontal meridian.

The measurements of heterophoria are recorded as prism diopters of deviation. To standardize the two instruments for these measurements, all were done at a distance of approximately 15 feet (457 cm.). The effect of accommodation on the aniseikonic state of the subject has purposefully been omitted. The measurement of heterophoria on the eikonometer is accomplished by means of a polaroid system of projection of a red dot on a grid. The more discerning subjects had considerable difficulty in separating entirely the images through this polaroid system, even though reduced light was used. The comparator compensates for the factor of heterophoria by rotation of one of the projection units. The position of the two projected images then becomes a function of the angle of deviation between the two eyes.

The targets used were the standard eikonometer target, subtending an angle of 4 arc degrees on the eye, and the usual comparator target, which subtends an angle of 39 minutes. The angle subtended by the eikonometer target (4 degrees) has been found to be the most satisfactory in the experience of the Dartmouth group [4]; i. e., it seems to permit the patient to recognize size differences most readily and still

4. Gliddon, G. H.: Lectures at Dartmouth Eye Institute, 1941.

falls within the macular area of fixation. Some investigators[5] feel that working with an angle of 8 arc degrees produces an effect of heterophoria or heterotropia which is part of the picture of the condition being measured on the eikonometer. The comparator has perhaps alleviated some of this objection by diminishing ocular motility in the examination; however, the limits of tolerance, or sensitivity to size difference, appear to be more gross than on the eikonometer.

The rather consistent heterophoria measured in most cases, which usually seemed most pronounced when there was considerable size difference, is another indication of the close relationship between aniseikonia and the heterophorias.[6] In clinical experience this relationship has been established in the minds of some ophthalmologists to such an extent that, from the practical standpoint, they feel that the correction of the heterophoria is perhaps a prerequisite to the alleviation of asthenopic symptoms thought to be caused by aniseikonia.

The results of the study, as presented in the accompanying table, may be summarized as follows:

Case 1.—The comparator revealed a size difference in one meridian in the left eye and slight esophoria. The eikonometer revealed no size difference and no heterophoria. The patient was more sensitive to size difference with the eikonometer.

Case 2.—The comparator revealed a spherical magnification combined with a cylindric magnification, right hyperphoria and slight exophoria. The eikonometer revealed only a cylindric size difference, no vertical deviation and pronounced exophoria.

Case 3.—The results with the two instruments checked closely as to both spherical and cylindric size difference. Slight hyperphoria was revealed with each and slight exophoria with the comparator. No horizontal deviation was shown with the eikonometer.

Case 4.—The results with the two instruments checked closely as to size difference. The eikonometer was more sensitive. The comparator showed left hyperphoria and the eikonometer right hyperphoria. Both instruments revealed esophoria. The subject had many asthenopic symptoms.

Case 5.—The spherical and the cylindric magnification were greater with the comparator. Right hyperphoria was shown by the comparator, with practically no size difference in the vertical meridian with the eikonometer. Slight exophoria was shown with each instrument. The limits of recognition of size differences were much closer with the eikonometer.

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5. Friedenwald, J. S., and others: Personal communication to the author.

6. It has been the experience of the members of the Department of Aniseikonia at Northwestern University Medical School that practically all patients referred to that department show by measurements with the eikonometer or the comparator a heterophoria of such dimensions as to warrant correction. These patients have practically all been selected by competent ophthalmologists to be studied for aniseikonia after a thorough examination, in which the Maddox rod has frequently failed to uncover the heterophoria.

CASE 6.—A size difference was revealed with the comparator but not with the eikonometer. Practically no heterophoria was shown with either instrument. The limits of recognition of size differences were much closer with the eikonometer.

CASE 7.—The comparator showed mixed magnification in the two eyes. The eikonometer showed spherical and cylindric magnification in the left eye. The former instrument revealed hyperphoria and exophoria and the latter only exophoria. The subject complained of asthenopia.

CASE 8.—Magnification in the left eye was revealed at 180 degrees by the comparator and at 90 degrees by the eikonometer. The comparator revealed right hyperphoria and the eikonometer no deviation.

CASE 9.—Practically no magnification was shown with either instrument. The comparator revealed right hyperphoria and the eikonometer no deviation.

CASE 10.—The comparator showed a magnification in the left eye both spherical and meridional; the eikonometer, only a magnification at axis 90 in the right eye. The comparator revealed right hyperphoria and esophoria and the eikonometer no deviation.

CASE 11.—Magnification in each eye was shown with the comparator. The eikonometer showed only magnification at axis 90 in the right eye. Slight right hyperphoria was revealed with the comparator and no deviation with the eikonometer.

CASE 12.—Magnification both spherical and cylindric was greater with the comparator than with the eikonometer, with the limits of recognition of size differences much farther apart with the former. The comparator revealed slight exophoria and the eikonometer none.

CASE 13.—The comparator revealed chiefly a spherical magnification; the eikonometer, meridional correction. The comparator showed slight hyperphoria and exophoria and the eikonometer no deviation.

CASE 14.—With both instruments there was practically no size difference. The comparator showed slight hyperphoria and esophoria and the eikonometer no deviation.

CASE 15.—The comparator showed spherical correction with a slight cylindric correction and hyperphoria as well as esophoria. The eikonometer revealed no size difference and no deviation. The patient had asthenopic symptoms.

CASE 16.—The two instruments showed close agreement as to size differences, and both revealed practically no deviation.

CASE 17.—The instruments were in close agreement as to size difference. The comparator revealed both a vertical and a horizontal heterophoria and the eikonometer no deviation.

CASE 18.—The comparator showed more cylindric magnification and vertical heterophoria. The eikonometer revealed only a spherical size difference and no deviation.

CASE 19.—The comparator showed a large meridional size difference and the eikonometer a negligible size difference. The comparator revealed a vertical and a horizontal heterophoria and the eikonometer only a horizontal heterophoria. The patient had asthenopic symptoms.

CASE 20.—The comparator showed mixed meridional size differences and the eikonometer a size difference only in the left eye. Heterophoria was not shown with either instrument.

CASE 21.—There was close agreement as to size difference; vertical heterophoria was revealed by both instruments. The comparator also showed a horizontal heterophoria.

CASE 22.—A negligible size difference and a vertical heterophoria were revealed with each instrument.

CASE 23.—A greater spherical size difference was shown with the comparator. The comparator revealed hyperphoria and the eikonometer only exophoria.

CASE 24.—The comparator showed mixed meridional size differences and the eikonometer a meridional difference in only one eye. The comparator revealed a vertical heterophoria. The patient had asthenopic symptoms.

CASE 25.—The comparator showed a meridional size difference, while the eikonometer did not. The comparator revealed a slight vertical heterophoria, while the eikonometer showed no deviation.

SUMMARY

Twenty-five subjects were measured for aniseikonia under similar circumstances, two instruments, the eikonometer and the comparator, being used for the purposes of comparison.

In only 1 instance (case 10) was there a great disagreement between the two instruments. It would seem that since in this case the size difference was manifested at 180 degrees in one eye on the comparator and at 90 degrees in the other eye of the eikonometer, the case was one of "induced size effect." [7]

A note of the heterophoria revealed by the two instruments has been made. The frequency with which heterophorias are associated with size differences as measured on the two instruments is rather startling.

Of the 25 subjects studied, 15 showed a hyperphoria of more than 0.50 prism diopters with the comparator, while only 4 of these showed a vertical deviation of 0.50 prism diopters or more with the eikonometer.

The predominance of right hyperphoria as shown with the comparator suggests that some of the heterophoria produced may be artificial, caused by a pull due to fixation on the edge of shutters of the instrument. A reversal in direction of the movement of the shutters should verify this explanation.

CONCLUSIONS

1. A patient is more sensitive to small size differences as created by the aniseikonic units with the eikonometer than with the comparator.

2. Heterophoria—both vertical and horizontal—is found more frequently and is of greater amount with the comparator than with the eikonometer.

3. There is a close relationship between heterophorias and the condition called aniseikonia. The comparator offers a possibility of segregating these two elements.

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7. Ogle, K. N.: Induced Size Effect, Arch. Ophth. **20**:604-623 (Oct.) 1938.

4. Neither instrument in its present stage of development is able to overcome entirely the problem of segregating the size difference between the two eyes from heterophorias and establishing it as a definite mathematical error responsible for the difficulties in binocular vision in a given case.

Fundamentally, the conclusion from this study is that size differences are more readily identified with the eikonometer, while the comparator utilizes what is fundamentally a mechanical parallax screen cover method of determining heterophorias.

HYPERSENSITIVENESS OF THE MUCOUS MEMBRANE

III. SLIT LAMP STUDIES OF THE CONJUNCTIVAL REACTIONS INDUCED IN NORMAL AND IN ATOPIC PERSONS WITH HISTAMINE, ETHYLMORPHINE AND ATOPENS

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The skin presents obvious obstacles to a satisfactory study of the detailed changes which occur in the vascular responses involved in specific and nonspecific wheal formation. The accessibility of the ophthalmic mucosa, with its visible blood supply, suggested the conjunctiva as an ideal site for the study of vascular reactions resulting from excitation with immunologic and nonspecific agents. With the aid of the slit lamp miscroscope, studies were undertaken to compare the characteristics of the specific and of the nonspecific reactions.

The ability of certain substances, antigenic and nonantigenic, to produce a conjunctival reaction is well known. Pollen extracts and other allergens almost regularly produce ophthalmic reactions in persons sensitive to them. Histamine and ethylmorphine, because of their ability to induce dilatation of the conjunctival vessels and even edema, are examples of nonspecific substances capable of eliciting a conjunctival reaction. Ethylmorphine, a derivative of morphine, is a vasodilator and lymphagogue. In the conjunctival sac it has a local anesthetic effect, causes a burning sensation in susceptible persons and in some persons induces sneezing due probably to irritation of the nasolacrimal passages. Its ophthalmic effects have not been completely studied or described. Histamine is a vasodilator, contracts unstriped muscle and lowers blood pressure.

ANALYSIS OF GROUPS STUDIED

The 69 patients studied were mainly young adults attending the clinics in allergy and ophthalmology (table 1). They were divided into four groups as follows:

Group 1, 19 subjects in whom the reaction of the atopic conjunctiva to specific excitation with antigen was observed. In this group there

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Presented at the fourth semiannual meeting of the Division of Allergy of the Jewish Hospital.

were (*a*) 11 subjects with hay fever who were naturally sensitive to ragweed pollen and (*b*) 8 subjects with the conjunctiva passively sensitized, that of 5 to ragweed and that of 3 to rabbit epithelium.

Group 2, 27 subjects, 10 normal and 17 allergic, on whom a solution of histamine was employed to produce an ophthalmic reaction.

Group 3, 15 subjects, 12 normal and 3 allergic, on whom a solution of ethylmorphine hydrochloride was used.

Group 4, a control group of 8 subjects. In 4 of these, naturally sensitive to pollen, physiologic solution of sodium chloride was instilled into the conjunctival sacs. In 4 normal, nonallergic subjects, pollen solution was employed.

TECHNIC

Prior to the instillation of the substance to be studied, the conjunctiva of each subject was observed with the binocular loupe and with the slit lamp, a no. 2 ocular lens and a no. A2 objective lens being used.

TABLE 1.—*Nature of Studies*

	Type of Ophthalmic Test				
	Specific Allergen				
Type of Conjunctiva	Ragweed	Rabbit Epithelium	Histamine	Ethylmorphine	Saline Solution
Naturally allergic	11	..	17	3	3
Passively sensitized in normal subjects	3	3	..	..	..
Normal: nonallergic	4	..	10	12	1

The patient was then placed in position at the slit lamp. The observer was seated at the oculars when the testing material was instilled into the eye, so as to be able to watch the initial response at the moment the reaction began. Whenever possible, the observer was left in ignorance of the particular excitant instilled. Reactions were studied for periods as long as three hours.

The nonspecific substances employed in the production of conjunctival reactions were solutions of histamine, 1 : 10,000 to 1 : 1,000, and solutions of ethylmorphine hydrochloride, usually 0.25 per cent. The specific allergic substances employed were ragweed pollen extracts, usually in a concentration containing 0.1 mg. per cubic centimeter of nitrogen, but in a weaker dilution when indicated. In normal subjects whose conjunctivas had been passively sensitized, an extract of rabbit epithelium containing 0.1 mg. per cubic centimeter of nitrogen was used to produce a reaction. From seven to fourteen days previously about 0.05 cc. of serum obtained from a person sensitive to rabbit epithelium had been injected into the conjunctivas of these subjects to produce local sensitization.

Briefly, the conjunctival vasculature presents two main networks, a superficial and a deep, with branches lying between them and connecting them at the limbus, posteriorly in the conjunctiva and also intra-

TABLE 2.—*Characteristics of Vascular Response of Conjunctiva to Excitation*

Type of Conjunctiva	Substance Used	Superficial Vessels	Deep Vessels	Sequence of Vessels Affected: Superficial Small	Superficial Large	Deep Small	Deep Large	Peri-corneal Sectors of Injection	Limbal Vessels
Naturally allergic	Specific allergen	+++	++++	2d	3d	4th	1st	+++	+++
	Histamine	++++	++++	2d	3d	4th	1st	0	++++
	Ethylmorphine	++	++++	2d	0	1st	3d	0	++++
	Saline solution (controls)	+	..	1st	0	2d	0	0	0
Normal: nonallergic	Specific allergens	+	..	1st	0	2d	0	0	0
	Histamine	++++	++++	2d	3d	4th	1st	0	++++
	Ethylmorphine	++	++++	2d	0	1st	3d	0	++++
	Saline solution	+	..	1st	0	2d	0	0	0
Passively sensitized in normal subjects		1. The results were identical with those in naturally allergic conjunctiva 2. Subcutaneous injection of the allergen produced a reaction similar to but milder than that produced by local instillation							

TABLE 3.—*Additional Characteristics of Conjunctival Reactions* *

Type of Conjunctiva	Substance Used	Edema of Conjunctiva	Epinephrine Hydrochloride (1:1,000), Effect †	Duration of Reaction ‡	Subjective Symptoms
Naturally allergic	Specific allergen	±	++++	++	Severe itching
	Histamine	+	++++	++++	Moderate burning
	Ethylmorphine	+++	++	+++	Slight burning
	Saline solution	0	..	..	0
Passively sensitized, in normal subjects	Specific allergen	..	++++	++	Slight to moderate itching
	Histamine	..	..	..	
	Ethylmorphine	..	..	..	
	Saline solution	..	..	..	
Normal nonallergic	Allergen	0	..	..	0
	Histamine	+	+++	++++	Moderate burning
	Ethylmorphine	+++	++	+++	Slight burning
	Saline solution	0	..	..	0

* No arterial contraction was observed during the reactions.
† The plus signs in this column represent the comparative degree of blanching, ++ indicating a mild and ++++ a severe degree.
‡ In this column ++ represents a moderate period (about one hour) and ++++ a prolonged period (two hours or more).

ocularly. Histologically, the larger conjunctival vessels are essentially the same as similar vessels elsewhere in the body.

The following features of the reactions were studied in detail: (1) the rapidity of onset of the vascular response to stimulation, (2) the order of such response on the part of the deep and of the superficial network of vessels, (3) the nature and frequency of vascular involvement among the vessels of the limbal and peripheral groups, (4) the presence or absence of edema, (5) the severity and duration of the

reaction, (6) the dilatation or contraction of vessels, (7) the effect of the instillation of a 1:1,000 solution of epinephrine hydrochloride and (8) the presence or absence of subjective symptoms.

RESULTS

In the first group, slit lamp examination of the conjunctival reactions produced with a solution of ragweed pollen in the 11 patients with sensitivity to that pollen revealed a definite sequence in the dilatation of the conjunctival vessels. The deep large vessels, the superficial fine vessels, the superficial large vessels and the deep fine vessels were involved in that order, the sequence occurring rapidly and uniformly. Practically no edema was present. Contraction of vessels was not seen in any subject. Pericorneal sectors of injection were frequently visible on gross inspection. Itching was a common subjective complaint.

In 6 nonallergic persons in whom the conjunctiva had been passively sensitized to ragweed or to rabbit epithelium from seven to fourteen days prior to testing, instillation of the related antigen produced a reaction similar to that obtained in the naturally sensitive subjects.

In 2 nonallergic subjects in whom the conjunctiva had been locally sensitized to ragweed pollen and in whom the reaction was induced by the subcutaneous injection of ragweed pollen into the arm, a similar ophthalmic reaction was obtained. However, it was weaker than that obtained by local instillation of the antigen into the passively sensitized conjunctiva, and associated subjective symptoms were weak or entirely absent.

The instillation of epinephrine hydrochloride solution produced constriction of the vessels in all of these reactions, as will be described presently.

As a control study, physiologic solution of sodium chloride was instilled into the eyes of 4 subjects, of whom 3 had hay fever and 1 was not allergic. The purpose was to observe the mechanical effect of merely instilling drops of a liquid into the eyes. An extremely faint reaction ensued, which developed rapidly but was evanescent. Some fine superficial vessels became visible but disappeared rapidly. This response bore no resemblance to the allergic reaction (or to the reaction to histamine and to ethylmorphine hydrochloride) and was apparently merely an irritative phenomenon. A similar response was obtained when drops of pollen solution were instilled into the conjunctival sacs of 4 nonallergic persons as a control test.

The subjects in group 2, 17 allergic and 10 nonallergic persons, were given conjunctival instillations of histamine phosphate solution. Identical results were obtained in the allergic and in the nonallergic subjects. The reaction developed rapidly and exhibited a diffuse dilatation of all superficial and deep vessels. There was probably a more

noticeable involvement of fine-branching superficial vessels in this type of reaction than in the specific type. The sequence in the vasodilation was the same in this reaction as in the specific reaction. Edema was infrequent and never more than moderate, even in severe reactions. Nevertheless, it was slightly more intense than in the specific response. Constriction of vessels was not observed at any time in the course of the reaction. There were no pericorneal sectors of injection, such as were noted in the reaction to pollen. The reaction faded more slowly than did the specific one. It was not accompanied by any subjective symptoms, except for an occasional slight burning sensation. The most outstanding characteristic was the pronounced tendency to dilatation of vessels, which appeared to be greater than in the specific response. The local effect of epinephrine hydrochloride in overcoming this dilatation was pronounced.

The subjects in group 3, 12 nonallergic and 3 allergic persons, were subjected to instillations of ethylmorphine hydrochloride solution. A definite variation from the results previously observed was noted. Although dilatation of the vessels resulted, its character was different from that seen in both the reaction to histamine and that to pollen. It came on as rapidly as in the reaction to histamine but faster than in the specific type. Ethylmorphine produced an immediate dilating effect, particularly on the deep network, both bulbar and limbal, with less effect on the superficial fine vessels. Pronounced edema always developed, and to a greater degree than with histamine or allergen. The slight burning sensation occasionally present was not as pronounced as in the reaction to histamine. There were no pericorneal sectors of injection. The response of allergic and that of normal eyes to ethylmorphine were similar in that, in both, the deep large and small vessels were affected most by dilatation, while the superficial vessels were only slightly involved. In the reaction to ethylmorphine the limbal vessels were affected more than the bulbar. The reaction faded more rapidly than the reaction to histamine but more slowly than the specific reaction. When it was severe, the layer of superficial vessels also became dilated. No contraction of vessels was seen at any time in the course of the reaction. Epinephrine hydrochloride was effective in counteracting the reaction. In short, ethylmorphine produced a reaction characterized mainly by dilatation of the deep vessels and pronounced edema, while in the reaction to histamine and the allergic reaction, both the superficial and the deep set were involved, with little edema.

COMMENT

Slit lamp inspection of the normal conjunctiva revealed a few isolated fine and moderate-sized superficial and deep vessels. In all types of reactions produced with specific and with nonspecific excitants,

innumerable vessels became visible which previously were not discernible. Vessels enlarged to several times their normal caliber, and movements of the blood columns appeared and disappeared as changes occurred in the size of the vessels. No constriction of vessels was discernible at any time, and dilatation of vessels appeared to be the rule. The latter may be explained by a local effect of the instilled substance on the vessel walls after absorption, possible by a liberation of histamine or H substance, by mechanical stimulation or by reflex action (Lewis). The tendency to enlargement of the deep vessels, seen in all the reactions, may be the result of absorption of the offending substance intraocularly and its retransmission externally to the deep set of conjunctival vessels by way of the system of anterior ciliary vessels. Part of the deep conjunctival dilatation may be due to drainage from the superficial set of conjunctival vessels. In 1 subject the fact that vessel dilatation occurred, was shown conclusively by a fascinating observation at the

TABLE 4.—*Summary*

Type of Excitant	Dilatation of Superficial Vessels	Dilatation of Deep Vessels	Pericorneal Sectors of Dilatation	Edema	Subjective Symptoms
Specific (19 subjects).....	+++	++++	+++	±	++++ (Itching)
Histamine (27 subjects).....	++++	++++	0	+	++ (Burning)
Ethylmorphine (15 subjects)....	++	++++	0	+++ or ++++	+ (Burning)
Saline solution (8 controls).....	±	0	0	0	0

site of a varicose conjunctival vessel. The varicosity joined a hairlike fine branch, in which a moving blood column could be seen. After instillation of histamine phosphate solution, the fine vessel became a dilated, large-sized vessel, as proved by the fact that the moving blood column disappeared, as usually happens when the vessel wall dilates or when the blood volume increases. The visible movement of blood cells also was obliterated. When epinephrine hydrochloride solution was instilled, constriction of the vessels followed throughout, and moving columns appeared and disappeared as the caliber and volume varied. The vessel previously described, which joined the varicosity and had been dilated by the effect of histamine, now began to show a moving column again, and slowly but definitely the wall became thinner and the caliber finer, until, finally, the vessel remained as a hairlike branch. This sequence corroborated the fact that dilatation had been present. Epinephrine manifested its action mainly on the conjunctival vessels, but primarily on the superficial network. After an interval, the deep network became constricted as a separate set. The action of epinephrine, therefore, finally resulted in the contraction of both sets of vessels.

SUMMARY

1. Because of its accessibility, the ocular mucosa provides an ideal location for study with the slit lamp. It offers opportunity for study with stereoscopic magnification, and reactions produced by instillations into the conjunctival sac may be followed from their incipience.

2. Vascular dilatation resulting from instillation with histamine and allergens involved the deep large vessels, the superficial fine vessels, the superficial large vessels and the deep fine vessels in that order. Dilatation after use of ethylmorphine hydrochloride involved mainly the deep network and then slightly the superficial vessels.

3. A solution of epinephrine hydrochloride 1 : 1,000 produced contraction of vessels equally after all types of reactions.

4. The reaction to histamine and the allergic reaction could not be differentiated by slit lamp observations.

5. Histamine and allergens dilate both the superficial and the deep vascular network to a marked degree.

6. Ethylmorphine hydrochloride dilates the deep vessels greatly and the superficial vessels only slightly.

7. There is no essential difference between the specific reaction induced in the naturally sensitive conjunctiva and that induced in the passively sensitized conjunctiva.

8. Itching was characteristic of the reaction to pollen, but was usually absent in the reaction to histamine and that to ethylmorphine. In the latter two reactions, subjective symptoms, when present, usually consisted of burning.

9. Injection of pericorneal sectors, when present, was associated with the specific reaction to pollen.

10. Control instillations of physiologic solution of sodium chloride or of pollen extract produced none of the characteristics of the reaction to ethylmorphine or to histamine or to the specific reaction.

CONCLUSIONS

1. Slit lamp microscopy reveals that the immediate conjunctival reactions induced by histamine and by specific antigens appear to be similar but differ from the type of reaction induced with ethylmorphine.

2. There is no evidence that muscular spasm plays any part in the allergic vascular reaction of the sensitive conjunctiva. The picture from its incipience was entirely one of vasodilatation.

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RESTORATION OF BINOCULAR VISION AFTER UNILATERAL CATARACT EXTRACTION

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It is usually considered that full correction cannot be worn after cataract extraction if the eye not operated on has normal vision. Most ophthalmologists (including myself) have made it a practice not to encourage patients with monocular cataract to have extraction done. This advice has been given because it has been felt that a correction could not be worn and the only advantage of the operation to the patient would be the cosmetic improvement and the increased field of vision. Ophthalmologists have neglected to have their patients make a fair trial with full correction to see whether it would be tolerated, because it has been felt that there was such a remote possibility of success.

This paper is written to create interest among ophthalmologists in carrying out a thorough trial with full correction.

Little information of a specific nature is found in textbooks or in the literature on this subject.

Duane [1] stated in a footnote that there have been cases in which full correction could be worn, and perhaps they are more frequent than is supposed.

Dianoux [2] found that full correction could be worn in some cases of cataract in which only one eye was operated on.

Little [3] reported a case of unilateral cataract in which the involved eye was operated on and later diverged markedly. Four years after the operation he corrected it with a contact lens. A prism was worn in the spectacle frame at first. Later binocular vision kept the eyes straight without a prism when the contact lens was worn.

McMullen [4] reported some cases of rather high anisometropia in which full correction was worn and stereoscopic vision obtained. The

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1. Duane, A., in Fuchs, E.: Text-Book of Ophthalmology, translated by A. Duane, ed. 4, Philadelphia, J. P. Lippincott and Co., 1911, p. 552.

2. Dianoux: Restitution de la vision binoculaire après extraction de la cataracte sur un seul oeil, Clin. opht. **23**:713, 1919.

3. Little, M. F.: Treatment of Unilateral Cataract with Contact Glasses, Arch. Ophth. **11**:646-650 (April) 1934.

4. McMullen, W. H.: Some Points in Anisometropia, Tr. Ophth. Soc. U. Kingdom (pt. 1) **59**:119-124, 1939.

greatest difference in refractive error between the two eyes was 7 D. None of these were cases of cataract.

Brown and others,[5] in commenting on a paper they abstracted, stated they had seen a woman who, after a lens extraction, wore a correction of + 2.50 D. sph. for the right eye and + 11.00 D. sph. for the left. Fusion was present, but no stereopsis. She experienced no discomfort when she wore the glasses.

Edward Jackson [6] reported 2 cases of cataract in which full correction could be worn. He [7] stated that "there seem to be no similar cases reported in the literature." In his first case, operation was performed forty years ago, when the patient was 42. The aphakic eye was only partially corrected at first, and then the correction was gradually increased until the following full correction was worn: right eye, + 11.00 D. sph. ⊃ — 1.37 D. cyl., axis 68 (vision 24/20); left eye, + 4.00 D. sph. ⊃ — 1.12 D. cyl., axis 80 (vision 24/20). In his second case, that of a man aged 63 on whom an operation for cataract had been performed by Dr. John H. Burleson, of San Antonio, Texas, the full correction was: right eye, + 2.25 D. sph. ⊃ 0.50 D. cyl., axis 84 (vision 1.2); left eye, + 11.00 D. sph. ⊃ — 2.50 D. cyl., axis 125 (vision 1.3). The patient was able to drive his automobile the next day when wearing his full correction. Both patients obtained binocular vision. Neither had any unpleasant symptoms when wearing full correction.

It is well known that some patients with anisometropia are able to wear full correction and others are not. Anisometropia of high degree occurs fairly commonly in patients with high myopia. A fair proportion of these patients can wear the full correction with comfort. Stereoscopic vision is usually present. In many, the anisometropia develops gradually, being due to unequal progression of the myopia in the two eyes. Thus the patient gradually becomes accustomed to the difference in correction of each eye due to repeated changes of glasses.

The following case is interesting, not only because the patient obtained binocular vision with depth perception but also because there was a foreign body (oxidized iron) in the lens. There was no satisfactory history of injury. Two roentgen examinations of the eye for a foreign body before operation gave negative results. After removal, it cast a definite, but not a dense, shadow on a dental x-ray film. Why it did not cast a more dense shadow was obscure to all who examined it.

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5. Brown, E. V. L., and others: The 1939 Year Book of Eye, Ear, Nose and Throat, Chicago, The Year Book Publishers, Inc., 1939, p. 243.

6. Jackson, E.: Tr. Am. Ophth. Soc., 1942, to be published.

7. Jackson, E.: Personal communication to the author.

REPORT OF A CASE

B. C., a 37 year old army officer, was admitted to Tilton General Hospital on Nov. 25, 1941 because of failing vision in the left eye of one month's duration. On October 20 he had been firing on the rifle range and thought some dust might have blown in his eyes. No history of a definite injury could be elicited, however. On October 21, while doing desk work, he found that he could not see well with the left eye. On October 30 he was admitted to another army hospital for observation. On examination there, his vision was found to be 6/6 in the right eye and 6/15 in the left. An immature cataract was found in the left eye. In the upper temporal portion of the lens, there was a small refractile body, which was suggestive of a foreign body. The family history was irrelevant, as was the patient's own history, except to reveal that when he was 11 years old he injured one of his eyes (he did not remember which one) by striking it on the tail gate of a wagon. No medical treatment was required for the injury.

The right eye appeared normal. The pupils reacted to light and accommodation. The left lens was opaque. There was a small refractile body in the upper temporal portion of the lens. The vision was 6/6 in the right eye and was reduced to perception of hand movements in the left. Light perception and projection were good in the left eye.

The tonsils showed evidences of chronic infection. Dental examination revealed a number of teeth with evidence of possible focal infection. Physical examination gave negative results in other respects.

Roentgen examination of the left eye for a foreign body gave negative results on two occasions.

Tonsillectomy was performed on December 8. The infected teeth were extracted later. On Jan. 8, 1942 the gums were fairly well healed.

On January 9 a linear extraction of the lens without iridectomy was performed. When the lens was "milked out," a brown, irregular-shaped foreign body came out with it.

The postoperative course was uneventful.

The foreign body was placed on a dental x-ray film, and then a roentgenogram was taken. The body cast a definite but not a dense shadow. Grossly, it had a rough surface and was friable. Chemical analysis showed that it contained iron oxide.

Refraction on January 27 gave the following results: right eye, $+0.25$ D. sph. $\bigcirc +0.25$ D. cyl., axis 145, vision 6/5; left eye, $+11.00$ D. sph. $\bigcirc +2.00$ D. cyl., axis 165, vision 6/5. With the addition of a $+4.00$ D. sph. before the left eye for near vision, the patient could read Jaeger type 1.

It had been explained to the patient before operation that he would be unable to wear a correction after operation. He was so pleased with his vision when refraction was performed that he got up and walked around the examining room with lenses in place in the trial frame. To my surprise he had no unpleasant symptoms, although both eyes were fully corrected. He insisted on having a full correction for both eyes ordered.

The correction described, with a cemented bifocal for the left eye, was ordered. He was able to wear this correction constantly and admitted no discomfort. Diplopia developed, however, when he looked to either side, up or down. A few days later he was tested with a stereoscope and found to have depth perception. It took him somewhat longer to "focus" with the stereoscope than it did the average patient.

After he got his glasses, he remained in the hospital for one month for completion of the necessary dental work (bridge work and dentures). He wore his glasses constantly during this time.

One case is not sufficient evidence on which to base definite conclusions. However, the result in this case was so satisfactory that I plan to attempt full correction in all cases in the future.

SUMMARY

1. Binocular vision with depth perception was obtained after cataract extraction in a case in which the eye not operated on was normal.

2. A metallic (iron) foreign body was present in the lens and was removed with it. No satisfactory history of injury could be obtained.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

SULFONAMIDE COMPOUNDS IN TREATMENT OF OCULAR INFECTIONS

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Since 1937 the sulfonamide compounds have been employed with success in the treatment of an increasing number of ocular infections, and an extensive literature has already accumulated in the few years since their introduction. In the present review I have attempted to summarize the significant literature and to evaluate in the light of available laboratory studies and personal experience the sometimes conflicting clinical results reported.

SULFONAMIDE COMPOUNDS AVAILABLE FOR CLINICAL USE

Since the introduction of the original prontosil by Domagk[1] in 1935, a large number of related compounds have been tested experimentally, but only a few have been found suitable for clinical use. In the United States only azosulfamide, sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) have come into general use in the treatment of ocular infections. Of these, azosulfamide and sulfapyridine have now been virtually discarded, the former because it is believed to have no action other than that conveyed by its sulfanilamide content, and the latter because of its relatively high toxicity. Of the remaining three drugs, sulfanilamide, sulfathiazole and sulfadiazine, the first has the advantage of greater solubility, which contributes to its better distribution throughout the ocular tissues; it has the disadvantage, however, of a comparatively high toxicity and of relative inactivity against such organisms as the pneumococcus and the staphylococcus. Of the latter two drugs, sulfadiazine appears to have a slight advantage over sulfa-

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1. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infectionen, Deutsche med. Wchnschr. **61**:250, 1935.

thiazole for oral use by virtue of its lower toxicity and is now considered the drug of choice for most general infections.[2] For local use sulfathiazole would seem to be the preferred drug on the basis of its higher in vitro activity.

It seems probable that topical application of the sulfonamide compounds will supplant in large part their oral use in ophthalmology. Such application will permit the employment of locally active drugs whose toxicity precludes their oral use. It is also probable that less toxic and more effective compounds will be introduced from time to time. Full chemical and pharmacologic data on the sulfonamide compounds are available in general reviews, such as that of Schnitker.[3]

DISTRIBUTION OF THE SULFONAMIDE COMPOUNDS IN THE OCULAR TISSUES

It is naturally of fundamental importance to know the concentration in the tissues of the eye of the various sulfonamide drugs obtainable by oral and topical medication. Little is known concerning the concentration in the human eye, but the results of the animal experiments of Bellows and Chinn,[4] Scheie and Souders,[5] Liebman and Newman,[6] Mengel,[7] Pinkhof,[8] P'an[9] and Gallardo and Thompson[10] are in general agreement that sulfathiazole and to a lesser degree sulfadiazine penetrate the intraocular tissues in lower concentrations than sulfanilamide or sulfapyridine but that inflammation and paracentesis facilitate this penetration.

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2. Chemotherapy in Infectious Diseases and Other Infections, Circular Letter 17, War Med. **2**:466 (May) 1942.

3. Schnitker, M. A.: Sulfonamide Compounds in the Treatment of Infections. New York, Oxford University Press, 1942.

4. Bellows, J. G., and Chinn, H.: The Distriblution of Sulfanilamide in the Eye, J. A. M. A. **112**:2023 (May 20) 1939; Penetration of Sulfathiazole in the Eye, Arch. Ophth. **25**:294 (Feb.) 1941. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, ibid. **27**:34 (Jan.) 1942.

5. Scheie, H. G., and Souders, B. F.: Penetration of Sulfanilamide and Its Derivatives into Aqueous of the Eye, Arch. Ophth. **25**:1025 (June) 1941.

6. Liebman, S. D., and Newman, E. H.: Distribution of Sulfanilamide and Its Derivatives Between Blood and Aqueous, Arch. Ophth. **26**:472 (Sept.) 1941.

7. Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:406 (Sept.) 1939.

8. Pinkhof, J.: The Content of Sulfanilamido-Pyridine (M. & B. 693) in the Ocular Fluids of Rabbits After Administration of the Drug, Ophthalmologica **97**: 356, 1939.

9. P'an, S. Y.: Distribution of Sulfanilamide in the Ocular Fluids and Tissues After Local Application, Proc. Soc. Exper. Biol. & Med. **46**:31, 1941.

10. Gallardo, E., and Thompson, R.: Sulfonamide Content of Aqueous Humor Following Conjunctival Application of Drug Powders (Effect of Inflammation), Am. J. Ophth. **25**:1210, 1942.

The data of Scheie and Souders [5] are of particular interest in that the levels of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine in the blood and in the aqueous of the cat are compared. Thus twenty-four hours after ingestion of single doses of the drugs, the primary aqueous showed 78.7 per cent of the level of sulfanilamide in the blood; the percentage was 81.4 for sulfapyridine, 18.4 for sulfathiazole and 75.0 for sulfadiazine. Sulfathiazole was even held back in the secondary aqueous, reaching only 59.2 per cent of the level in the blood, whereas the concentration of sulfadiazine in the secondary aqueous reached 80.3 per cent. Although one must be cautious in applying data derived from animals to human beings, it would seem justifiable on the basis of this evidence to use sulfadiazine in preference to sulfathiazole for intraocular infections.

METHODS OF ADMINISTRATION

Ocular infections rarely if ever require intravenous or subcutaneous administration of the sulfonamide drugs. Oral therapy remains the standard method of administration, the usual dose being such as to maintain a concentration in the blood of 5 to 10 mg. per hundred cubic centimeters. For staphylococcic infections it is desirable to maintain a concentration of at least 10 mg., because of the relatively high resistance of this organism. The dose required to maintain the 5 to 10 mg. level averages about 0.1 Gm. per kilogram of body weight given in divided doses every four to six hours. A simple method, advocated by Long,[11] is to give, to adults, an initial dose of 4.0 Gm., then maintenance doses of 1.0 Gm. every four hours for the first twenty-four hours and then doses of 1.0 Gm. every six hours, modifying these doses according to determinations of the level in the blood.

The sulfonamide compounds can be used locally in solution, powder, ointment or emulsion form. Sulfanilamide is used in an 0.8 per cent concentration in physiologic solution of sodium chloride, while sulfathiazole and sulfadiazine, because of their low solubility, are employed in 5 per cent concentrations (isotonic) of their sodium salts. The alkalinity of the sodium salts may produce slight conjunctival irritation. Sulfanilamide and sulfadiazine powder are well tolerated in the conjunctival sac. Sulfathiazole crystals, unless broken up and sifted through fine mesh, are somewhat irritating, but the new microcrystal preparation [12] should be much less so. The ointments are well tolerated on

11. Long, P. H.: The Clinical Use of Sulfanilamide, Sulfapyridine, Sulfathiazole, Sulfaguanidine, and Sulfadiazine in the Prophylaxis and Treatment of Infections, Canad. M. A. J. **44**:217, 1941.

12. Chambers, L. A.; Harris, T. N.; Schumann, F., and Ferguson, L. K.: The Use of Microcrystals of Sulfathiazole in Surgery, J. A. M. A. **119**:324 (May 23) 1942.

the lids and in the conjunctival sac and are generally employed in 5 per cent strength, although lower concentrations have often proved effective and higher concentrations can be used without irritation in many patients. Emulsions and jellies have the advantage of releasing the drug more rapidly than ointments.

The nature of the ointment or emulsion base is of considerable importance, particularly for infections of the lid margins. In a recent report, Pillsbury, Wammock, Livingood and Nichols[13] described an effective vehicle for use on the skin as one which would (1) retain the sulfonamide compound in a finely divided state at the site of application for a reasonable period, (2) permit close contact of the compound with the site of infection, (3) be miscible with serous and purulent drainage, (4) not form an impermeable and inert covering under which bacteria might grow readily and (5) permit easy removal of bacteria contained in crusts and surface debris. They stated that all-grease bases, such as petrolatum, hydrous wool fat or ointment U. S. P., are effective in retaining a medicament at the site of application but may not allow intimate contact of the antiseptic agent with the site of infection, do not mix readily with exudate, are sometimes removed with difficulty and probably increase the growth of bacteria under the film of grease. They stated that they prefer an oil in water emulsion type of base in which the sulfonamide compound is first suspended or dissolved in the external aqueous phase, believing that it offers certain advantages, including evenly distributed contact with the site of the infection, a low surface tension, ability to mix readily with exudate and easy removal by washing. They reported favorable results also with a stearate vanishing type of base, which, while it is, they said, more satisfactory than the grease type, is still inferior to the emulsion type. Favorable results were obtained with both these types in the treatment of primary superficial cutaneous infections of pyogenic origin.

Braley and I,[14] in a recent study on the treatment of catarrhal conjunctivitis, found that a hydrous wool fat–petrolatum base allowed longer persistence of sulfathiazole in the conjunctival sac than other bases. For use on the conjunctiva when rapid dilution of the drug with tears is a factor, the grease base would seem to have this important advantage over the emulsion or the jelly type of base, but for the skin of the lids or lid margins the emulsion type would appear to be more valuable.

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13. Pillsbury, D. M.; Wammock, V. S.; Livingood, C. S., and Nichols, A. C.: The Local Treatment of Pyogenic Cutaneous Infections with Sulfathiazole in an Emulsion Base, Am. J. M. Sc. **202**:808, 1941.

14. Thygeson, P., and Braley, A. E.: Local Therapy of Catarrhal Conjunctivitis with Sulfonamide Compounds, Arch. Ophth. **29**:760 (May) 1943.

Powder can be used best in the treatment of hospitalized patients with corneal ulcer, and sulfadiazine powder would seem to be preferred at present. The powder is dusted or blown by a powder blower into the conjunctival sac as often as necessary, usually about every three to four hours. Powder is the most effective medication to be used locally for conjunctival and corneal infections but unfortunately is not practical for use in the treatment of ambulant patients.

Solutions of sulfanilamide, sodium sulfathiazole and sodium sulfadiazine have been employed locally in the conjunctival sac, but the rapid dilution and elimination of the drug by the tears render extremely frequent instillations necessary for any significant therapeutic results. Since the sulfonamide drugs have a bacteriostatic rather than a bactericidal action, a continuous therapeutic concentration at the site of the lesion is a necessity.

Local therapy with a sulfonamide compound can be combined with oral therapy in the treatment of severe infections. Recently Boyd [15] and von Sallmann [16] have advocated the use of iontophoresis in order to obtain higher concentrations of the sulfonamide compounds in the cornea, aqueous and anterior part of the uvea than can be obtained by other means. This method, in which a 5 per cent sodium sulfathiazole or, preferably, sodium sulfadiazine solution is usually employed, has been used with success in the treatment of experimental Bacillus pyocyaneus ulcer of the rabbit and in the treatment of a number of infections of man, including ulcer and endophthalmitis. To obtain the maximum effect, iontophoresis is best employed in conjunction with oral administration and local application of powder.

TOXIC MANIFESTATIONS OF THE SULFONAMIDE COMPOUNDS

According to Long [11] the only contraindication to the use of a sulfonamide drug is a previous toxic reaction to it. Before the oral use of one of the drugs is instituted the patient must always be asked about previous experience, and if a history of a toxic reaction is obtained a small test dose of the drug (0.15 to 0.3 Gm.) can be given and the patient observed for twelve hours. If there is any sign of toxicity it is best to employ a different compound in treating the patient, as cross sensitivity between the various compounds is unusual.

When sulfathiazole, sulfapyridine or sulfadiazine is employed, the urinary output should be kept at a minimum of 1,000 cc. per day to minimize precipitation of the acetylated drug, which is more likely to

15. Boyd, J.: Sodium Sulfathiazole Iontophoresis, Arch. Ophth. **28**:205 (Aug.) 1942.

16. von Sallmann, L.: Sulfadiazine Iontophoresis in Experimental Pyocyaneus Ulcer of the Rabbit Cornea, Am. J. Ophth. **25**:1292, 1942.

occur in a concentrated urine. Furthermore, the urine should be kept neutral or alkaline to litmus paper because of the low solubility of the sulfonamide compounds and their tendency to precipitate under acid conditions. Renal calculi are perhaps the most alarming complication which can occur with these preparations.

Mild toxic reactions from the sulfonamide compounds occur frequently and dangerous reactions infrequently. The drugs are undoubtedly being used more commonly than is warranted, but when definitely indicated they should be employed without hesitation. As advocated by Long,[11] a patient receiving a sulfonamide compound should be seen every day and symptoms of toxicity noted. The physician should examine the scleras carefully for jaundice and the conjunctivas for paleness as a sign of anemia. If the conjunctivas are pale and the scleras jaundiced hemolytic anemia is probably developing; while if the conjunctivas are not pale the jaundice probably results from hepatic damage. Inquiry as to the development of sore throat should be made, since the occurrence of sore throat during the course of therapy with a sulfonamide compound may indicate the beginning of agranulocytosis. The skin should be examined for the occurrence of a rash and the patient should be warned to keep out of the sun during the period of therapy to avoid a cutaneous reaction on the basis of photosensitization. The temperature should be taken frequently for detection of drug fever. Laboratory checks should consist of blood counts, determinations of the level of drug in the blood and examinations of the urine. If a severe toxic reaction occurs use of the drug should be discontinued and fluids forced.

No general toxic reactions are to be expected from the local use of the sulfonamide compounds, but local allergic reactions occur not infrequently. Sensitivity to sulfathiazole ointment has been observed in about 0.5 per cent of the cases at Presbyterian Hospital in which the ointment has been used continuously over a long period.

Except for local allergic reactions, ocular toxic manifestations are rare and not serious. Transitory myopia,[17] retinal hemorrhages[18] and a single case of optic neuritis,[19] temporary in character, have been reported. Haviland and Long[20] described 6 patients with an episcleral and conjunctival injection restricted in the main to the exposed portions

17. Bristow, J. H.: Temporary Myopia Due to Sulfanilamide, Arch. Ophth. **24**:799 (Oct.) 1940.

18. Goar, E. L.: Retinal Hemorrhages Following the Ingestion of Sulfathiazole, Am. J. Ophth. **25**:332, 1942.

19. Bucy, P. C.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

20. Haviland, J. W., and Long, P. H.: Skin, Conjunctival, and Scleral Reactions in Course of Therapy with Sulfathiazole, Bull. Johns Hopkins Hosp. **66**:313, 1940.

of the bulbar conjunctiva in a group of 78 patients treated with sulfathiazole. In 4 of the 6 patients the lesion occurred in the conjunctiva with severe dermatitis. The reaction disappeared within forty-eight hours after withdrawal of the drug.

SUPPLEMENTAL THERAPY

The action of the sulfonamide compounds can be enhanced by specific serotherapy, a procedure which has been followed with success in the treatment of the pneumococcic pneumonias for which type serums are available. Other serums which might be used in conjunction with the sulfonamide compounds include staphylococcus antitoxin,[21] meningococcus antiserum or antitoxin, gas gangrene antitoxin and streptococcus antitoxin. No reports are as yet available as to results obtained with this type of combined therapy in the treatment of ocular infections, but there is reason to believe it would be useful in the prophylaxis and treatment of staphylococcic or pneumococcic intraocular infections.

It has been shown experimentally, both in vitro and in vivo, that the bacteriostatic action of the sulfonamide compounds is enhanced by an increase in temperature. Thus patients with urethral gonorrhea resistant to a sulfonamide compound have yielded to a sulfonamide compound plus fever therapy. There would, therefore, seem to be a definite place in ophthalmology for combined sulfonamide compound and fever or foreign protein therapy in the control of fulminating infections of the cornea or the inner eye.

The in vitro action of the sulfonamide compounds has been increased by azochloramid [22] and by oxidizing agents, such as hydrogen peroxide, zinc peroxide and urea peroxide.[23] It is possible that such potentiation of local action of sulfonamide compounds may prove of great value in the treatment of external ocular infections, but no clinical studies are as yet available.

CHEMOTHERAPY OF VIRUS INFECTIONS OF THE EYE

As is now well known, none of the typical viruses are affected by any of the sulfonamide drugs. There are, however, four viruses of the psittacosis–lymphogranuloma venereum group, a group of atypical viruses forming a connecting link between the typical large viruses and the Rickettsiae, which are sulfonamide sensitive. Three of these, the

21. Kolmer, J. A., and Brown, H.: Chemotherapy and Chemoserotherapy of Staphylococcic Infections, Arch. Int. Med. **69**:636 (April) 1942.

22. Schmelkes, F. C., and Wyse, O.: Inactivation of Sulfonamide Inhibition by Azochloramid, Proc. Soc. Exper. Biol. & Med. **49**:263, 1942.

23. Thompson, M. R.: Personal communication to the author.

viruses of trachoma, inclusion conjunctivitis, and lymphogranuloma venereum, are known to cause significant ocular lesions.

Trachoma.—Following the initial reports of Loe,[24] Lian,[25] Dik [26] and Kirk, McKelvie and Hussein,[27] a large number of reports on the treatment of trachoma with sulfonamide compounds have appeared. These may be divided into three main groups: (1) those [28] that claim a fair

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24. Loe, F.: Sulfanilamide Treatment of Trachoma: Preliminary Report, J. A. M. A. **111**:1371 (Oct. 8) 1938.

25. Lian, B.: Sulfanilamide in the Treatment of Trachoma, Geneesk. tijdschr. v. Nederl.-Indië **78**:1614, 1938.

26. Dik, J. H. R.: Use of Prontosil and Uliron in Ophthalmology, Geneesk. tijdschr. v. Nederl.-Indië **78**:1614, 1938.

27. Kirk, R.; McKelvie, A. R., and Hussein, H. A.: Sulfanilamide in Treatment of Trachoma, Lancet **2**:994, 1938.

28. (*a*) Loe.[24] (*b*) Forster, W. G.: Treatment of Trachoma with Sulfanilamide, Am. J. Ophth. **23**:532, 1940. (*c*) Richards, P.; Forster, W. G., and Thygeson, P.: Treatment of Trachoma with Sulfanilamide, Arch. Ophth. **21**:577 (April) 1939. (*d*) Gradle, H., in discussion on Loe.[24] (*e*) Thygeson.[32] (*f*) Rambo, V. C.: Proc. All-India Ophth. Soc. **6**:193, 1938. (*g*) Lech Junior: Quimioterapia no trachoma, Arq. Inst. Penido Burnier **5**:164, 1939. (*h*) Heinemann: A Case of Trachoma, Geneesk. tijdschr. v. Nederl.-Indië **77**:1967, 1937. (*i*) Kirk, McKelvie and Hussein.[27] (*j*) Burnet, E.; Cuenod, E., and Nataf, R.: Essai de chimiothérapie du trachome par un dérivé glucosé du "4:4' diaminodiphénylsulfone," Arch. Inst. Pasteur de Tunis **28**:11, 1939. (*k*) Hatschek, G.: Experiences with Different Sulfanilamide Preparations in Treatment of Trachoma, Acta ophth. orient. **1**:243, 1939. (*l*) Jasseron, F., and Morard, G.: La chimiothérapie du trachome par la para-amino-phényl-sulfamide (1162 F), Bull. Soc. d'opht. de Paris **51**:212, 1939; Le traitement du trachoma par les dérivés sulfamidés en particulier la p-amino-phényl-sulfamide en ingestion, Presse méd. **48**:234, 1940. (*m*) Shimkin, N. I.: Treatment of Trachoma with Sulfanilamide, Acta ophth. orient. **1**:251, 1939. (*n*) Spearman, M. P., and Vandevere, W. E.: Sulfapyridine in Trachoma, J. A. M. A. **113**:1807 (Nov. 11) 1939. (*o*) Wilson W. A.: Sulfanilamide Treatment of Trachoma, Am. J. Ophth. **22**: 674, 1939. (*p*) Zachert, M.: Antistreptin in Treatment of Trachoma, Klin. oczna **17**:428, 1939; abstracted, Am. J. Ophth. **22**:1424, 1939. (*q*) Lee, O. S., Jr., and Rottenstein, H.: Trachoma Treated with Sulfanilamide and Its Derivatives, J. A. M. A. **115**:107 (July 13) 1940. (*r*) Cooper, W. L.: Management of Recurrent Trachoma Following Sulfanilamide Therapy, Arch. Ophth. **24**:467 (Sept.) 1940. (*s*) Cosgrove, K. W.: Trachoma Problems in Arkansas, South. M. J. **34**:1037, 1941. (*t*) Cosgrove, K. W., and Hundley, L. K.: The Use of Various Sulfanilic Acid Derivatives in Trachoma, ibid. **35**:43, 1942. (*u*) Luo, T. H., and Chang, E.: Sulfanilamide in Treatment of Trachoma, Chinese M. J. **58**:512, 1940. (*v*) Kettler, J. R., and Rutherford, C. H.: Sulfanilamide in Old Trachoma, J. Indiana M. A. **33**:227, 1940. (*w*) Tiscornia, A.; Moret, R. L., and Just Tiscornia, B.: La sulfanilamido en el tratamiento de las complicaciones del tracoma, Arch. de oftal. de Buenos Aires **14**:825, 1939. (*x*) McCoy, D., in Presentation of Clinical Eye Cases from the Los Angeles County General Hospital, Am. J. Ophth. **22**:1410, 1939. (*y*) Gradle, H. S.: Visual Results in the Trachoma Clinics of Southern Illinois, J. A. M. A. **119**:792 (July 4) 1942.

percentage of complete and permanent cures of this disease, (2) those [29] that claim pronounced improvement in the disease but few if any permament cures without supplementary therapy and (3) those [30] that claim little if any effect on the disease. The reports in the first two groups are well in the majority, and there can be no doubt now that sulfanilamide has proved to be a therapeutic agent of great value.

There is still disagreement as to the action of the sulfonamide compounds, whether on the virus itself or on a secondary bacterial infection. I feel certain from my own experience with bacteriologically controlled uncomplicated trachoma that the action of the drug is directly on the virus, probably in preventing multiplication rather than in viricidal effect. The report of Julianelle and Smith [31] indicates that exposure of trachoma virus in infected tissues to sulfanilamide for periods up to five hours does not remove its infective capacity for monkeys. This result is what one would expect from a drug which is known to have a bacterio-

29. (*a*) Dejean, C., and Roux, J.: Traitement du trachome par certains composés sulfamidés en injections sous-conjonctivales, Bull. Soc. d'opht. de Paris **51**: 202, 1939. (*b*) Guyton.[50] (*c*) Hirschfelder, M.: Treatment of Trachoma with Sulphanilamide, Am. J. Ophth. **22**:299, 1939. (*d*) Schwarz, J.: Over de resultaten van een ondersteuing der localé trachoomtherapie door middel van Sulfanalamide en Anthromaline, Geneesk. tijdschr. v. Nederl.-Indië **79**:1971, 1939; cited by Smith, Julianelle and Gamet.[291] (*e*) Szinegh, B.: Beiträge zur Chemotherapie des Trachoms, Arch. f. Ophth. **141**:109, 1939. (*f*) Harley, R. D.; Brown, A. E., and Herrell, W. E.: Sulphanilamide and Neoprontosil in Treatment of Trachoma, Am. J. Ophth. **23**:662, 1940. (*g*) Poleff, L.: Sur l'application des sulfamides dans le traitement du trachome, Presse méd. **48**:235, 1940. (*h*) Julianelle, L. A.; Lane, J. F., and Whitted, W. P.: Effect of Sulfanilamide on Course of Trachoma, Am. J. Ophth. **22**:1244, 1939. (*i*) Smith, J. E.; Julianelle, L. A., and Gamet, J. H.: Sulfonamide Therapy of Trachoma, ibid. **24**:174, 1941. (*j*) McKelvie, M. B.; Kirk, R., and Holder, H. J.: Observations on the Chemotherapy of Trachoma, ibid. **24**:1035, 1941. (*k*) Que, K. L.: Economical Value of Sulfanilamid in Therapy of Trachoma, Ophthalmologica **99**:479, 1940. (*l*) Rychener, R. O.: Trachoma Treated with Sulfanilamide, Memphis M. J. **13**:158, 1938.

30. (*a*) Richards, P.: Sulphonamide Chemotherapy of Trachoma, Mem. Ophthalmic Lab., Giza, Ann. Rep. (1937) **12**:103, 1938. (*b*) Busacca, A.: Quelques essais de thérapeutique du trachome par les composés sulphamidiques du trachome, Rev. internat. du trachome **16**:168, 1939; Risultati ottenuti con l'impiego di preparati solfamidici e di diidrofollicolina in alcune forme congiuntivali ed in altre affezioni oculari, Folia clin. et biol. **10**:198, 1938. (*c*) Cavara, V.: La terapia sulfamidica nel campo oftalmologica, Boll. d'ocul. **18**:597, 1939. (*d*) Jebejian, R.: Quelques observations sur l'effet des sulfamides par voie interne dans le trachome, Ann. d'ocul. **176**:671, 1939. (*e*) MacCallan, A. F.: Sulphonamide Treatment of Bacterial and Trachomatous Conjunctivitis, Brit. M. J. **1**:482, 1940. (*f*) Spining, W. D.: Some Observations on Use of Sulfanilamide in Trachoma and Associated Ocular Conditions, Am. J. Ophth. **23**:271, 1940. (*g*) Sory, R.: Sulfanilamide in Trachoma Therapy, ibid. **25**: 713, 1942.

31. Julianelle, L. A., and Smith, J. E.: Studies on the Infectivity of Trachoma: The Effect of Sulfanilamide on the Virus, Am. J. Ophth. **25**:317, 1942.

static rather than a bactericidal action. My [32] findings in inclusion conjunctivitis, which is an entirely analogous virus disease, are of interest in that the virus could still be demonstrated by baboon inoculations and by the finding of inclusion bodies during the first two to three days of chemotherapy. A treatment time of five days or longer was required to effect a cure.

It is difficult to account for some of the failures reported, but in any attempt to do so the reports should be analyzed according to reliability of diagnosis, sulfonamide compound used, adequacy of dosage, duration of treatment and occurrence of secondary factors in the production of inflammation, especially deficiency of tears, secondary infection, trichiasis and xerosis.

It is obvious that mistakes in the diagnosis of trachoma are still being made in spite of the fact that the slit lamp and corneal microscope have greatly improved the reliability of diagnosis through the determination of incipient pannus. The disease is still being confused with certain types of severe keratoconjunctivitis of bacterial origin, with chronic follicular conjunctivitis, with ocular pemphigus, with old vernal catarrh showing radium cicatrization and occasionally with the keratoconjunctivitis of molluscum contagiosum. Furthermore, the great majority of reports do not discriminate between the trachoma itself and the inflammation caused by the secondary factors enumerated. It is not yet known which of the sulfonamide drugs is most active against the disease, but a guess may be hazarded that the discrepancies in the results reported were not so much due to the type of drug as to the question of dosage and duration of treatment. Indeed, in my opinion inadequate therapy can be held responsible for most of the failures or recurrences reported.

The 70 cases of trachoma treated at the Vanderbilt Clinic and the Institute of Ophthalmology of Presbyterian Hospital form a small but unique series in that they have been analyzed completely with respect to the factors outlined. To this end all cases in which trachoma was suspected were divided into four groups: (1) those in which there were all the clinical signs plus Halberstaedter-Prowazek inclusions, (2) those in which there were the clinical signs but in which no inclusions were found, (3) those in which there was probably trachoma but in which an unequivocal diagnosis could not be made and (4) those in which there was either conjunctival scarring or pannus which was probably not trachomatous and could be explained on the basis of pemphigus, surgical intervention, application of radium, etc. Sulfanilamide therapy was extraordinarily successful in this series, and long term results have

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32. Thygeson, P.: The Treatment of Trachoma with Sulfanilamide, Am. J. Ophth. **23**:679, 1940.

more than borne out the claims made in the preliminary report [32] for groups 1, 2 and 3, and, on the other hand, as was anticipated, there was no improvement in any of the cases in the fourth group. It can be said with reasonable certainty that the sulfonamide compound rendered the disease inactive in all cases of active trachoma in this series with the exception of 3 in which inadequate treatment was administered because of toxic reactions. In 4 cases there was persistent conjunctival inflammation which could be accounted for on the basis of bacterial infection, tear deficiency or trichiasis. Repeated epithelial scrapings in these cases failed to show Halberstaedter-Prowazek inclusion bodies, an evidence of trachomatous activity, although in 2 of these cases the bodies were observed prior to the institution of chemotherapy. To my knowledge there have at the time of writing been no recurrences among the cases of healed infection, in most of which a follow-up examination was made at monthly intervals for a year after healing and has been made at three or six month intervals since then.

The success obtained in this series is believed to have been due to adequate dosage and treatment time. In my opinion no set dosage or treatment time can be specified for trachoma and the treatment schedules outlined by Loe [24] and by most other reporters are inadequate. In the Vanderbilt Clinic series the patients were treated until the trachoma was believed to be inactive as indicated by the condition of the cornea. Experience has shown that the disappearance of corneal infiltrates and, most important of all, the disappearance of punctate fluorescein-staining lesions so characteristic of active trachoma, are indications that treatment can safely be discontinued, irrespective of the persistence of conjunctival or limbal follicles, which sometimes require many weeks to become absorbed.

The importance of dosage and treatment time is well illustrated by the results obtained in 18 additional cases of trachoma in children at Letchworth Village, a state mental institution near New York city. It was not possible for me to treat these patients personally or to determine the levels of drug in the blood, and low doses of sulfanilamide (30 to 45 grains [2 to 3 Gm.] daily) were prescribed for a fourteen day period. Pronounced improvement was obtained in every case, but permanent cure required one or more additional courses of treatment in all but 4 cases. That low doses over a long period can be curative was illustrated by a case of stage III trachoma with extensive and progressive pannus which healed completely and permanently with a daily dose of 20 grains (1.3 Gm.) of sulfanilamide for seven weeks. In general, however, it appears to be advisable to maintain a blood level of at least 3 mg. per hundred cubic centimeters of blood.

In view of my experience with sulfanilamide in the treatment of trachoma since 1938, I feel that the drug is definitely curative in uncomplicated trachoma when properly administered and that only for trachoma complicated by severe secondary infection, particularly of the lid margins, or by tear deficiency, trichiasis, etc., is supplementary treatment required. Sulfapyridine, sulfathiazole and sulfadiazine are also curative, but there are as yet incomplete data on their relative values. Dr. Polk Richards,[33] medical director in charge of trachoma activities for the Indian Service, whose experience covers more than 4,000 sulfanilamide-treated patients, expressed the opinion that sulfadiazine is at least as efficacious. By analogy with bacterial infections, in which sulfathiazole and sulfadiazine are relatively more efficient than sulfanilamide, it seems safe to assume that these drugs will prove superior in trachoma likewise.

Inclusion Conjunctivitis.—The literature on therapy with sulfonamide compounds is more uniform as to results obtained for this virus disease than for trachoma. Favorable results have been recorded by McKelvie,[34] Thygeson,[35] Allen,[36] Giddens and Howard,[37] Lugossy,[38] Braley [39] and Thygeson and Stone.[40] Only Lugossy reported equivocal results. In my experience the disease has responded rapidly and completely to oral administration of sulfanilamide, sulfathiazole or sulfadiazine, and permanent cures could be obtained with treatment times as short as a week.

Thygeson and Stone [40] reported satisfactory results in 11 cases of inclusion blenorrhea of the newborn from 5 per cent sulfathiazole ointment used six times a day. The patients recovered almost as rapidly as those receiving oral therapy. Local treatment was not as successful in adults, supplementary oral therapy being required in some instances. This difference in response to local therapy may be related to differences in tear function: In the newborn there are few if any tears to dilute the medication. More frequent local applications of the sulfonamide compound in adults would seem to be indicated.

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33. Richards, P.: Personal communication to the author.

34. McKelvie, A. R.: Ophthalmic Report, Annual Report of the Sudan Medical Service, 1938, p. 67; cited by McKelvie, Kirk and Holder.[29j]

35. Thygeson, P.: Sulfanilamide Therapy of Inclusion Conjunctivitis, Am. J. Ophth. **22**:179, 1939; Treatment of Inclusion Conjunctivitis with Sulfanilamide, Arch. Ophth. **25**:217 (Feb.) 1941.

36. Allen, J. H., in discussion on Bucy.[19]

37. Giddens, S. W., and Howard, W. A.: Inclusion Blennorrhea in Pediatric Practice, M. Ann. District of Columbia **9**:333, 1940.

38. Lugossy, J.: Chemotherapy in Paratrachoma, Ophthalmologica **100**:68, 1940.

39. Braley, A. E., in discussion on Thygeson, P., and Stone, W., Jr.: Epidemiology of Inclusion Conjunctivitis, Arch. Ophth. **27**:91 (Jan.) 1942.

40. Thygeson, P., and Stone, W., Jr.: The Treatment of Inclusion Conjunctivitis with Sulfathiazole Ointment, J. A. M. A. **119**:407 (May 30) 1942.

While oral therapy of inclusion conjunctivitis is eminently successful, it seems unwise in the treatment of a benign, self-limited disease to subject the patient to even the slight risks of severe toxic reactions. Local therapy, combined only if necessary with oral therapy, would therefore seem to be the treatment of choice.

Lymphogranuloma Venereum.—Infection of the eye with lymphogranuloma venereum virus has been reported by a number of investigators and may appear either as a primary lesion or as a secondary manifestation of previous genitourinary disease. In the literature there are 6 cases of severe conjunctivitis in which the virus of lymphogranuloma venereum was proved to be the cause. Two are of special interest. The first, a case of primary ocular infection reported by Curth, Curth and Sanders,[41] was an instance of keratoconjunctivitis of six years' duration simulating Parinaud's conjunctivitis. Although useful vision was lost owing to corneal cicatrization, sulfanilamide by mouth taken irregularly over a period of four months resulted in the disappearance of conjunctival discharge and inflammatory signs. In the second case, an instance of accidental infection in a laboratory worker, reported by Oliphant, Powell and Perrin,[42] there was an acute conjunctivitis which failed to respond to the usual forms of therapy but healed completely on ten days' treatment with sulfadiazine in a dose of 3 Gm. daily. A corneal ulcer believed to be due to the virus but not so proved was reported by Meyer and Reber [43] to have healed rapidly with sulfanilamide therapy.

There are now a large number of reports on the treatment of the venereal manifestations of lymphogranuloma venereum with sulfonamide compounds, and the majority claim favorable results. Sulfanilamide has proved satisfactory in many cases, but sulfathiazole and sulfadiazine seem to be the preferred compounds.

CHEMOTHERAPY OF BACTERIAL INFECTIONS OF THE EYE

The sulfonamide drugs have a wide range of activity against many of the bacteria causing ocular infections. This action varies with the different bacteria, from high activity against the beta hemolytic streptococcus to low activity against the staphylococcus. For chronic infections it may be desirable to test the infecting organism against the

41. Curth, W.; Curth, H. W., and Sanders, M.: Chronic Conjunctivitis Due to the Virus of Venereal Lymphogranuloma, J. A. M. A. **115**:445 (Aug. 10) 1940.

42. Oliphant, J. W.; Powell, W. F., and Perrin, T. L.: Sulfadiazine in Lymphogranuloma Venereum Ophthalmitis, J. A. M. A. **118**:973 (March 21) 1942.

43. Meyer, G. P., and Reber, J.: A Case of Corneal Ulcer Associated with Lymphogranuloma Venereum, Am. J. Ophth. **24**:161, 1941.

various sulfonamide compounds by in vitro methods in order to choose the most active drug. For acute infections it is wisest to use either sulfathiazole or sulfadiazine in preference to sulfanilamide because of their wider range of activity and lower toxicity.

Gonorrheal Ophthalmia.—Sulfonamide compounds have been extraordinarily successful in the treatment of gonococcic infections. The now extensive literature indicates that clinical and bacteriologic cure without complications within a week is to be expected in adequately treated patients who are seen before ulceration occurs. Of particular interest is the report of Lewis,[44] who treated 120 patients with three of the sulfonamide compounds and compared the results obtained with those for 50 patients treated prior to the introduction of specific chemotherapy. The accompanying table, taken from his article, illustrates clearly the superiority of sulfapyridine and sulfathiazole over sulfanilamide and of

Gonococcic Conjunctivitis: Comparison of Results With and Without a Sulfonamide Compound (from Lewis[44])

	Number of Cases	Average Number of Days for Care	Average Number of Days in Hospital	Unsatisfactory Results *
Presulfanilamide therapy	50	17.3	20.3	18
Sulfanilamide	90	5.4	8.9	8
Sulfapyridine	22	2.57	4.85	0
Sulfathiazole	8	4.0	6.0	1

* Cases of visual damage from corneal ulceration, relapse and slow clinical and bacteriologic cure are placed under this heading.

chemotherapy over the therapy used before the introduction of sulfonamide compounds. A similar conclusion as to the superiority of sulfathiazole over sulfanilamide was reached by Wong[45] in a study of 40 patients. The 5 patients who have been treated at the Institute of Ophthalmology, 4 with sulfanilamide and 1 with sulfathiazole, all recovered rapidly and without complications.

Local treatment has been tried with apparent success by Rein and Tibbetts[46] and by Penneton.[47] The former investigators used sulfanilamide solution for irrigation in treating 15 patients who recovered without complications; the latter used sulfanilamide powder with equally

44. Lewis, P. M.: Gonococcic Conjunctivitis, J. A. M. A. **117**:250 (July 26) 1941.

45. Wong, R. T.: Chemotherapy in the Treatment of Gonorrheal Ophthalmia, Arch. Ophth. **27**:670 (April) 1942.

46. Rein, W. J., and Tibbetts, O. B.: Irrigation with Sulfanilamide as a Treatment for Gonorrheal Conjunctivitis, Am. J. Ophth. **22**:112, 1939.

47. Penneton, P.: Local Treatment of Gonorrheal Conjunctivitis with Sulfanilamide Powder, Am. J. Ophth. **24**:314, 1941.

good results. The success obtained in the treatment of catarrhal conjunctivitis by topical application of sulfonamide compounds certainly warrants further exploration of this method for all types of conjunctivitis, but the seriousness of gonococcic infection more than justifies the slight risks entailed in oral administration. There is no reason why oral therapy cannot be combined with local therapy to advantage, however, and for this purpose sulfadiazine is probably preferable to sulfathiazole because it is better tolerated, both locally and systemically. The powder can be used in the conjunctival sac without significant irritation. The 0.8 per cent solution of sulfanilamide in physiologic solution of sodium chloride can be used as an irrigation fluid to remove exudate during the first day or so of therapy, but little therapeutic effect can be expected from it unless it is used frequently, because of its rapid dilution by tears. Solutions of the sodium salt of sulfathiazole or of sulfadiazine have not been recommended because of their alkalinity and possible deleterious effect on the corneal epithelium, but in my opinion this danger has been exaggerated. In 5 per cent concentrations such preparations are well tolerated.

The results obtained in ocular gonorrhea have seemed substantially superior to those reported for the urethral disease. This fact may be related to anatomic considerations, which make chronic ocular gonorrhea a great rarity. No cases of ocular gonorrhea resistant to sulfonamide compounds have as yet been reported, although Guyton and Woods [48] mentioned 2 cases in which the disease was resistant to sulfanilamide but cleared promptly in response to sulfapyridine. It has thus not been necessary to employ supplementary foreign protein or fever therapy for resistant ocular infection, as has been done for the genitourinary disease, but it is well to know that a potentially effective combination therapy is available.

At present sulfathiazole appears to be the drug of choice in the treatment of the urethral disease, but it is possible that sulfadiazine may displace it, since satisfactory reports, such as that of Parsons,[49] describing 100 per cent of cures in 30 consecutive cases, are appearing.

Streptococcic Infections.—Beta hemolytic streptococcus infections of the eye include erysipelas and streptococcic impetigo of the lids, acute and chronic dacryocystitis, conjunctivitis, corneal ulcers and panophthalmitis and are for the most part severe and dangerous in character. As was to have been expected from results obtained in streptococcic infections elsewhere in the body, most ocular infections have responded

48. Guyton, J. S., and Woods, A. C.: Use of Sulfanilamide in Ophthalmology, Am. J. Ophth. **24**:428, 1941.

49. Parsons, R. P.: Estimate of Sulfadiazine in Treatment of Gonorrhea, U. S. Nav. M. Bull. **40**:13, 1942.

readily to sulfonamide compounds. In their review on the sulfonamide compounds in ophthalmology, Guyton and Woods [48] described 9 cases of beta hemolytic streptococcus infection, including 2 of panophthalmitis, 5 of infection of the lids or orbit and 2 of corneal ulcers, in all of which the disease responded promptly. Guyton [50] previously reported from the Wilmer Ophthalmological Institute a case of purulent endophthalmitis (beta hemolytic streptococcus), 2 cases of lid infection and 1 case of socket infection, in all of which the infection healed rapidly with sulfanilamide. A purulent panophthalmitis following injury necessitated evisceration in spite of therapy. Jones [51] reported favorable results in the treatment of streptococcic orbital cellulitis. Swan and Allen [52] reported 3 cases of severe pseudomembranous conjunctivitis which was caused by hemolytic streptococci and responded readily to sulfanilamide. An orbital cellulitis of mixed streptococcic and pneumococcic causation, reported by Swigert,[53] was healed by means of sulfanilamide.

At the Institute of Ophthalmology, cases of beta hemolytic streptococcus infection have included 1 case of erysipelas of the lids, 1 of acute dacryocystitis, 2 of membranous conjunctivitis, 6 of catarrhal conjunctivitis and 1 of central corneal ulcer. The infection healed rapidly in response to a sulfonamide compound in all cases except 1 of severe membranous conjunctivitis in which the patient when first seen had necrosed corneas and extensive conjunctival destruction. Sulfanilamide, and later sulfadiazine, used both orally and locally, failed to affect the course of the disease, and streptococci persisted in the lesion for over three weeks. The organism was a group A type 25 streptococcus which was susceptible to the sulfonamide compounds in vitro. The failure of chemotherapy is believed to have been due to a possible antisulfonamide action of broken-down tissue products. Removal of necrotic tissue, by surgical means if necessary, would appear to be indicated in such cases.

There are few data available on the chemotherapy of ocular infections caused by streptococci of the anaerobic, viridans or nonhemolytic varieties. According to Long,[11] Streptococcus viridans infections should be susceptible and the other two resistant. Catarrhal conjunctivitis probably caused by Str. viridans has responded to 5 per cent sulfathiazole ointment according to Thygeson and Braley.[14]

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50. Guyton, J. S.: The Use of Sulfanilamide Compounds in Ophthalmology, Am. J. Ophth. **22**:833, 1939.

51. Jones, C.: The Use of Sulfanilamide in Otolaryngology and Ophthalmology, Iowa State M. J. **29**:6, 1939.

52. Swan, K. C., and Allen, J. H.: Streptococcic Pseudomembranous Conjunctivitis Treated with Sulfanilamide, Am. J. Ophth. **22**:1255, 1939.

53. Swigert, L.: Orbital Cellulitis Treated with Sulfanilamide, Am. J. Ophth. **23**:86, 1940.

Staphylococcic Infections.—Staphylococcic infections of the eye are probably the most frequent as well as the most important of all ocular infections. All parts of the eye and adnexa are attacked, but blepharitis, conjunctivitis and marginal corneal ulcers are the most frequent infections. It is unfortunate that the organism, as compared with the gonococcus and the hemolytic streptococcus, is relatively resistant to the sulfonamide drugs. Sulfathiazole is the preferred drug, and high concentrations in the blood are required for effective therapy. Topical application has proved of value for the external infections, notably blepharitis and conjunctivitis.

Guyton and Woods [48] have reported 7 instances of staphylococcic panophthalmitis. Of these, the infection in all responded well to a sulfonamide compound except 2 of the 3 in which sulfanilamide was used. At the Institute of Ophthalmology there have been 7 cases of staphylococcic intraocular infection; the response to a sulfonamide compound was satisfactory in 4 and slow in 2, and in 1 there was no response. These results are encouraging but not completely satisfactory. The use of sulfathiazole or sulfadiazine iontophoresis, as suggested by Boyd [15] and von Sallmann,[16] combined with adequate oral therapy plus local application of powder should give the maximum chemotherapeutic effect. Additional supplementary therapy could include staphylococcus antitoxin and foreign protein or fever therapy.

I [54] have reported favorable results in the treatment of staphylococcic blepharitis with 5 per cent sulfathiazole ointment. Infections of recent onset or without deep involvement of the meibomian glands responded more readily than those of long duration. For best results the medication had to be used four to six times daily and its use had to be combined with other measures, including epilation of infected cilia, expression of the meibomian glands and administration of staphylococcus toxoid. Staphylococcic impetigo and infectious eczema of the lids responded rapidly and completely to 5 per cent sulfathiazole ointment.

With Braley, I [14] reported favorable results in the treatment of acute staphylococcic conjunctivitis with 5 per cent sulfathiazole ointment. Chronic staphylococcic conjunctivitis responded more slowly and necessitated thorough treatment of the lid margins even in the absence of obvious blepharitis. As has been pointed out by a number of observers, infection of the lid margins is responsible for the chronicity of staphylococcic conjunctivitis, and conjunctival treatment alone will not effect a cure.

Guyton and Woods [48] reported 2 staphylococcic infections of the lids treated by oral administration of sulfapyridine which healed slowly.

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54. Thygeson, P.: Staphylococcic Blepharitis, Tr. Am. Acad. Ophth. (1941) **46**:265, 1942.

I have found oral use of sulfathiazole of little value in lid margin infections, but sulfathiazole ointment has proved of value in the management of recurrent hordeola.

Staphylococcic corneal ulcers are for the most part a complication of blepharoconjunctivitis or conjunctivitis and have responded reasonably well to local therapy with sulfonamide compounds. In my experience with 42 cases, sulfadiazine powder used every three to four hours in the conjunctival sac proved to be superior to either sulfathiazole or sulfadiazine in ointment form. To prevent recurrences the preexisting conjunctivitis or blepharitis must be eliminated.

The report of Moore, Gardner, Bell and Tannenbaum [55] described a case of thrombophlebitis of the cavernous sinus of staphylococcic origin cured by sulfathiazole. Concentrations ranging from 25 to 33 mg. per hundred cubic centimeters were maintained during the six day critical period of the disease. The authors stated the belief that the high concentrations of the drug were responsible for the favorable outcome.

Pneumococcic Infections.—In their review, Guyton and Woods [48] recorded only 3 pneumococcic infections, 1 a purulent conjunctivitis which healed rapidly with sulfapyridine and 2 corneal ulcers which gave a doubtful response to sulfapyridine and required supplementary local treatment. Johnstone,[56] on the other hand, reported favorable results in 41 cases in which sulfapyridine powder was used locally; in most instances, however, he also employed cauterization. Others who reported favorable results included Szinegh,[57] who used sulfapyridine by mouth; Rosengren,[58] who used sulfapyridine successfully in 6 cases, and Roggenkämper,[59] who employed sulfanilamide only as an auxiliary measure. Chamberlain [60] reported 5 cases in which sulfapyridine by mouth failed to give unquestionable results. Of 3 pneumococcic ulcers treated with sulfapyridine at the Institute of Ophthalmology, 2 healed readily and 1 improved greatly but required supplementary therapy. One treated with sulfanilamide did not improve.

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55. Moore, G. B.; Gardner, J. D.; Bell, K. R., and Tannenbaum, A. J.: Cavernous Sinus Thrombophlebitis, J. A. M. A. **119**:708 (June 27) 1942.

56. Johnstone, I. L.: Sulphonamide Treatment of Hypopyon Ulcer of the Cornea, Brit. M. J. **1**:887, 1941.

57. Szinegh, B.: Der Wert der Chemotherapie in der Behandlung des Ulcus serpens corneae, Arch. f. Ophth. **141**:300, 1939.

58. Rosengren, B.: Treatment of Ulcus Serpens Corneae with M & B 693, Acta ophth. **17**:209, 1939.

59. Roggenkämper: Hornhautulkus und Prontosil, Klin. Monatsbl. f. Augenh. **103**:211, 1939.

60. Chamberlain, W. P., Jr.: Treatment of Pneumococcal Corneal Lesions, Arch. Ophth. **27**:869 (May) 1942.

The failure of sulfapyridine administered orally to influence pneumococcic ulcers satisfactorily was also shown in the experimental ulcers produced by Chamberlain,[60] who demonstrated that good concentrations of the drug were present in the corneas. It is probable that in the avascular cornea, in which the prompt leukocytic reactions of vascular tissues are lacking, high concentrations of the drug are required. Oral therapy plus local therapy with powder would seem to be indicated. For fulminating ulcers supplementary sulfathiazole or sulfadiazine iontophoresis might prove of great value.

There is little information available on the chemotherapy of pneumococcic panophthalmitis. The 1 patient at the Institute of Ophthalmology was treated with sulfanilamide prior to the introduction of sulfapyridine and failed to respond.

Pneumococcic conjunctivitis is benign and responds to simple therapy, but sulfathiazole ointment is believed to shorten its course.[14] Healing generally requires only a few days when the 5 per cent ointment is used four to six times daily. The 1 patient of Guyton and Woods responded rapidly to oral therapy with sulfapyridine, as did a patient with type XIX pneumococcus ophthalmia reported on by Millett.[61]

B. Pyocyaneus Ulcer and Panophthalmitis.—B. pyocyaneus (Pseudomonas aeruginosa) is a cause of fulminating corneal ulcer and may rarely cause panophthalmitis and meibomianitis. Therapy has been extremely unsatisfactory, most affected eyes being lost. The value of sulfapyridine in the treatment of experimental B. pyocyaneus ulcer of the rabbit was shown by Joy.[62] More recently Robson and Scott[63] reported the effectiveness of sodium sulfacetimide used locally in the treatment of experimental ulcer, while von Sallmann[16] described even more favorable results when sulfadiazine iontophoresis was used to obtain high corneal concentrations of the drug.

Favorable results with sulfapyridine in the treatment of B. pyocyaneus ulcer in human beings have been reported by Lepard,[64] and Stone and I[65] described the successful use of sulfadiazine given orally

61. Millett, J.: Sulfapyridine in Pneumococcus Type XIX Ophthalmia, New York State J. Med. **40**:1389, 1940.

62. Joy, H. H.: Sulfapyridine in Experimental B Pyocyaneus Ulcer, Proc. Soc. Exper. Biol. & Med. **45**:709, 1940; Treatment of Experimental Bacillus Pyocyaneus Ulcer of Cornea with Sulfapyridine, Arch. Ophth. **27**:1135 (June) 1942.

63. Robson, J. M., and Scott, G. I.: Local Effectiveness of Sodium Sulphacetamide (Albucid Soluble) in Treatment of Experimental Ulcers of the Cornea, Brit. M. J. **1**:5, 1942.

64. Lepard, C. W.: B. Pyocyaneus Ulcer: Report of Three Cases, Tr. Am. Acad. Ophth. **46**:55, 1941.

65. Thygeson, P., and Stone, W., Jr.: New York State J. Med., to be published.

combined with sulfadiazine powder. In view of the favorable results recorded in the treatment of experimental infections, early diagnosis and treatment with the sulfonamide compounds would seem to be clearly indicated.

Guyton and Woods [48] reported failure in the treatment of a patient with B. pyocyaneus panophthalmitis with sulfanilamide, and equally unsatisfactory results were obtained with oral use of sulfathiazole at the Institute of Ophthalmology. It seems obvious that with a fulminating infection of this type good results can be expected only when treatment is instituted early and when the best drug is chosen. Sulfathiazole and sulfadiazine are the most bacteriostatic members of the group but penetrate the eye only poorly. For both ulcer and intraocular infection with B. pyocyaneus it would seem desirable to obtain high concentrations in the blood to supplement the oral therapy with application of powder in the conjunctival sac, combined with iontophoresis when possible.

Haemophilus Influenzae Infections.—The influenza bacillus is a cause of conjunctivitis, dacryocystitis and rarely orbital cellulitis. The organism is known to be sensitive to the sulfonamide compounds, but the sensitivity is low, comparable to that of the staphylococcus. Guyton and Woods [48] reported a case of acute dacryocystitis, of corneal ulcer and of acute purulent conjunctivitis, in all of which the infection healed rapidly with oral use of a sulfonamide compound. In the experience of Thygeson and Braley,[14] H. influenzae conjunctivitis has responded well to treatment with 5 per cent sulfathiazole ointment.

Diplobacillary Conjunctivitis and Corneal Ulceration.—Thygeson and Braley,[14] in their study of catarrhal conjunctivitis, found that both the Morax-Axenfeld and the nonliquefying type of diplobacilli responded to therapy with 5 per cent sulfathiazole ointment.

Miscellaneous Bacterial Infections.—The meningococcus is a rare cause of conjunctivitis and endophthalmitis and is highly susceptible to therapy with sulfonamide compounds. Guyton and Woods [48] reported a case of meningococcic panophthalmitis which responded dramatically to sulfanilamide. According to Long,[11] the preferred drug in the treatment of meningococcic infection is sulfanilamide. Even if sulfathiazole or sulfadiazine should prove to have equal or slightly greater bacteriostatic properties, the higher intraocular concentrations obtainable with sulfanilamide would still make this drug preferable for intraocular infections due to the meningococcus.

Colon bacilli and related organisms which may occasionally cause conjunctivitis are susceptible to therapy with sulfonamide compounds, use of powder and ointment forms of sulfathiazole and of sulfadiazine constituting the treatments of choice.

Bacteria of the Proteus group are a rare cause of conjunctivitis and are also susceptible to sulfonamide compounds, but no clinical data are available on the response of ocular infections. One patient at the Institute of Ophthalmology became clinically well with oral sulfathiazole therapy, but the infection recurred. Sulfathiazole ointment was then applied and improved but did not cure the condition.

Friedländer's bacillus (Klebsiella pneumoniae) may be found in cases of chronic dacryocystitis and of acute ulcer. One case of meibomianitis in which the organism was found in the glands has been observed at the Institute of Ophthalmology. The organism is susceptible to the sulfonamide compounds, and sulfadiazine appears to be the drug of choice. The one ulcer I have observed responded well to sulfadiazine administered orally combined with powder applied locally. For fulminating ulcer sulfadiazine iontophoresis would be of value.

CHEMOTHERAPY OF UVEITIS

Sulfonamide compounds appear to be of little or no value in the treatment of uveitis. Guyton and Woods [48] reported failure in 27 cases, in 14 of which the infection was probably gonococcic. The Institute of Ophthalmology figures list 11 cases, in only 2 of which there was significant improvement. In 2 cases of sympathetic ophthalmia sulfadiazine and sulfathiazole failed to bring about improvement in spite of the fact that favorable results had been reported by Gamble.[66]

RARE INFECTIONS SUSCEPTIBLE TO CHEMOTHERAPY

Clostridium welchii panophthalmitis following a perforating wound of the globe is a distinct entity and has been reported from many parts of the world. The organism is sensitive to sulfonamide compounds, though to a low degree, but since all eyes affected by it have progressed to enucleation or evisceration, the sulfonamide compounds should certainly be given a trial. According to Long,[11] sulfanilamide is the drug of choice. Oral therapy combined with local application of powder would seem to be indicated. C. welchii antitoxin could well be used in conjunction with these procedures.

Chancroid [67] has proved unusually responsive to chemotherapy, both oral and local. Ocular infections are admittedly rare but should respond equally well to the sulfonamide compounds.

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66. Gamble, R. C.: A Case of Sympathetic Ophthalmia Treated with Sulfanilamide, Am. J. Ophth. **23**:1045, 1940; **24**:49, 1941.

67. Kornblith, B. A.; Jacoby, A., and Wishingrad, M.: Sulfanilamide in the Treatment of Chancroid, New York State J. Med. **39**:364, 1939.

Actinomycosis [68] involving the eyelids or orbit may prove to be amenable to sulfonamide compounds, according to a number of favorable reports which have appeared recently. It is noteworthy that the conjunctivitis secondary to Streptothrix concretions of the canaliculi cleared strikingly in 2 cases observed by me on the administration of sulfanilamide and sulfadiazine, although permanent cures were not obtained.

INFECTIONS PROBABLY NOT SUSCEPTIBLE TO CHEMOTHERAPY

Although brucellosis, tularemia and pemphigus have been reported as being susceptible to chemotherapy, later work indicates that they probably are not. A recent report [69] has suggested that syphilitic interstitial keratitis is responsive to sulfanilamide, but this is as yet uncomfirmed and there is nothing in previous clinical or experimental work to suggest that Spirochaeta pallida is susceptible to the sulfonamide compounds. Mooren's ulcer probably is not susceptible; in 3 cases at the Institute of Ophthalmology it failed to respond to intensive treatment. Blaess [70] and Szinegh,[57] however, reported favorable though not curative effects.

COMMENT

It is apparent that since 1938 the sulfonamide compounds have revolutionized the therapy of a number of ocular infections, including trachoma, inclusion conjunctivitis, lymphogranuloma venereum, gonorrheal ophthalmia, streptococcic pseudomembranous conjunctivitis, pneumococcic and streptococcic ulcer, B. pyocyaneus ulcer, erysipelas and impetigo of the lids and staphylococcic blepharoconjunctivitis. It is to be expected that the future will see a great extension of sulfonamide compound therapy in ophthalmologic practice. The promising fields appear to be (1) extension of topical application of the drugs in order to avoid the potential toxic reactions incident to oral therapy; (2) use of iontophoresis combined with oral and topical application to obtain maximum intraocular concentration of the drug in cases of corneal ulcer, endophthalmitis and panophthalmitis; (3) extension of the use of supplementary aids, such as fever or shock therapy and immunotherapy, and (4) potentiation of the local action of the compounds by oxidizing and wetting agents.[71]

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68. Cutting, W. S., and Gebhardt, L. P.: Inhibitory Effects of Sulfonamides in Cultures of Actinomyces Hormones, Science **94**:568, 1941.

69. Sandler, I. L.: Sulfanilamide Treatment of Syphilitic Interstitial Keratitis, Arch. Dermat. & Syph. **39**:528 (March) 1939.

70. Blaess, M. J.: Sulphanilamide in the Treatment of Mooren's Ulcer, J. Michigan M. Soc. **39**:249, 1940.

71. Goldberger, H. A.: Potentiation of Sulfonamide Derivatives by Oxidants in Local Therapy of Wounds, Am. J. Surg. **56**:353, 1942.

The sodium salt of sulfathiazole and of sulfadiazine in powder form have been employed topically in the treatment of experimental and clinical wound infections with success. It seems probable that sodium sulfathiazole and sodium sulfadiazine powder, in spite of their alkalinity, can be employed for corneal ulcer and for endophthalmitis. These salts have a distinct advantage over the acids in their markedly greater solubility, which allows rapid release of the drugs. Although frequent applications of the powders would be necessary, it is probable that high corneal and intraocular concentrations would be obtainable. Although there is no evidence to indicate that concentrations of the sulfonamide drugs beyond a minimum effective level further retard bacterial growth, sulfonamide inhibitors, such as one might expect to find in corneal ulcer involving much cell destruction, can be neutralized by high concentrations of the drugs.

As judged by the accumulated literature, the most common errors in the treatment of ocular infections with sulfonamide componds are the use of oral therapy for conditions which are of such a minor character as not to warrant the risk of toxic reactions, and which are better controlled by local therapy, and the employment of inadequate doses and the failure to treat for a sufficient period of time. The latter error occurs particularly often in the treatment of trachoma, in which failure to obtain permanent healing is in my opinion a matter of inadequate therapy. Adequate therapy is predicated on the use of the most effective drug, with a therapeutic concentration maintained at the site of the infection for a period sufficient to produce complete eradication of the infecting agent.

SUMMARY AND CONCLUSIONS

Pertinent literature on the use of the sulfonamide drugs in ophthalmology is analyzed in the light of my personal experience with chemotherapy. It is concluded that these drugs properly employed should lead to rapid and complete healing of the majority of ocular infections caused by the viruses of trachoma, inclusion conjunctivitis and lymphogranuloma and by gonococcus, meningococcus, alpha and beta hemolytic streptococcus, staphylococcus (Staph. aureus), pneumococcus, influenza bacillus, diplobacillus, coliform rods, Friedländer's bacillus and pyocyaneus bacillus. Little or questionable effect is to be expected in brucellosis or tularemia and in infections due to nonhemolytic or anaerobic streptococci. No results are to be looked for in ocular infections such as ocular pemphigus, sympathetic ophthalmia, uveitis and ocular tuberculosis, syphilis and leprosy. Because of the occasional occurrence of mild or severe toxic reactions, oral therapy with sulfonamide compounds should not be used for minor infections and should be replaced by local therapy whenever possible.

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Correspondence

SULFONAMIDE COMPOUNDS IN OPHTHALMOLOGY

To the Editor:—In the Sept. 12, 1942 issue of the *British Medical Journal* (page 314) an editorial entitled "The Sulphonamides in Ophthalmology" summarized some of the recent publications on the value of the sulfonamide compounds in the treatment of ocular infections. May I point out some of the opinions which do not correspond with the ones I have found to exist?

The editorial stated:

> The sulphonamides, with their largely selective actions on the streptococcus, pneumococcus, meningococcus, and gonococcus, would not, therefore, appear to be promising in combating anything beyond the microbial infections of this type seen in the conjunctiva. . . . The most striking results are seen in ophthalmia neonatorum. . . . In practice sulphapyridine [2-(paraaminobenzenesulfonamido)-pyridine] proved remarkably effective in all types of ophthalmia neonatorum. . . . The results in ophthalmia neonatorum are so uniformly good that bacteriological examination to establish the identity of the causal organism is almost superfluous. . . .

The sulfonamide compounds are effective against not only the streptococcus, pneumococcus, meningococcus and gonococcus but a long list of other micro-organisms. It has been shown repeatedly that they are primarily not bactericidal but bacteriostatic. They must be present in sufficient concentration at the site of the infectious agent to be effective. Certain of the compounds have a greater bacteriostatic effect on particular strains of micro-organisms than others; for example, the staphylococcus is usually most susceptible to sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). In vitro studies have clearly shown that the susceptibility of the organism and the optimum concentration of the compound vary with the strain of organism and that certain drugs require a much higher concentration than others. The ideal way of handling a specific infection would be to obtain the organism in pure culture and test the effectiveness of a variety of the sulfonamide compounds against it. The variability in susceptibility of different organisms and strains may explain some of the unexpected failures and disappointments in clinical use of the drugs.

As to ophthalmia neonatorum, one would infer from the editorial that sulfapyridine is to be given orally in all cases. In practice sulfapyridine is effective against most types, but it is also the most toxic to the patient. Since the gonococcus responds to any of the sulfonamide compounds, one can choose the least toxic, which, at the present time, seems to be sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). If facilities are present for a laboratory diagnosis of the type of conjunctivitis present in the newborn infant, this should be carried out. Local therapy has proved almost as effective and certainly less dangerous than oral therapy, and the oral administration of sulfonamide compounds to the newborn infant should be reserved for the more serious infections, such as sometimes occur with the streptococcus. In the treatment of gonorrheal ophthalmia, inclusion conjunctivitis and staphylococcic conjunctivitis, a 5 per cent ointment of sulfathiazole or sodium sulfadiazine applied locally at frequent intervals is effective. It is not possible to maintain a bacteriostatic concentration of the drugs unless ointment is applied frequently. When a much higher concentration is needed, the local use of powder has proved effective.

The editorial further states that the value of treatment of staphylococcic infections of adults and older children has not been fully established. Staphylococcic infections, especially those associated with severe blepharitis, have responded better to local application of sulfathiazole than to any other form of treatment. In the majority of cases the infection is either cured or controlled by the use of 5 per cent sulfathiazole ointment. In the treatment of stubborn infection, the com-

bining of local use of a sulfonamide compound with administration of toxoid has been effective. In many cases there is associated meibomitis, which requires frequent expression as well as vigorous local therapy. One disadvantage of the frequent local use of sulfathiazole ointment is the high incidence of acquired sensitivity. Changing either to sulfadiazine or to sodium sulfacetimide (the sodium salt of N′-acetylsulfanilamide) in an ointment base is advisable.

The editorial further states: "Hypopyon keratitis, generally caused by the pneumococcus, often responds well to treatment, but failures are not uncommon." The failures can be explained by either one or both of two factors: first, the local concentration of the drug employed may be insufficient and, second, the pneumococcus may be of a type not susceptible to the sulfonamide compound. With regard to the first, some of the sulfonamide compounds, for example sulfathiazole, given orally are, practically, not absorbed by the eye. Sulfadiazine is absorbed, but perhaps in insufficient concentration. The oral use of sulfonamide compounds in the treatment of hypopyon ulcer, then, should be supplemented by the local use of powder or, when high concentrations are needed, by the introduction of the drug by iontophoresis. In all cases of hypopyon ulcer, it is advisable to obtain a culture and by in vitro methods test the organism obtained with various types of sulfonamide compounds.

The treatment of trachoma is summarized in the editorial as follows: ". . . . early reports raised hopes of a quick cure of this stubborn infection . . . but it would appear that the sulphonamides are merely a valuable adjuvant to the classical methods of treatment, acting, perhaps, only by their effect on the secondary infection which is almost always present." A good deal of conflicting literature has been accumulated. A recent series of over 4,000 carefully selected patients with trachoma have been treated by Dr. Polk Richards and his associates in the Indian Service with remarkable success; however, a recent communication from Dr. Wesley Forster, also of the Indian Service, stated that there is a type of conjunctivitis resembling trachoma in which neither inclusion bodies nor the severe corneal changes associated with true trachoma are present. In order to evaluate the results of sulfonamide therapy in trachoma, a positive clinical and laboratory diagnosis is certainly desirable. The infection that looks like trachoma but lacks some of its features does not respond to therapy with sulfonamide compounds. Some of the patients with trachoma were treated with insufficient amounts of drug. The disease seems to respond better to small doses given over a long period than to large doses employed for a short period. Certainly in a large series of proved cases of trachoma, the sulfonamide compounds did a great deal more than merely clean up the secondary infection.

The editorial further states: "Good results are also reported in herpes of the cornea." Experience has shown that proved herpes of the cornea does not respond to sulfonamide compounds, nor is experimental herpes affected by these drugs. None of the sulfonamide compounds seem to have any action against the herpes virus.

The editorial discusses infections produced by Bacillus pyocyaneus by saying: "Some work has also been done on *B. pyocyaneus* infection, but the evidence is conflicting." With this infection, careful analysis of the reports usually indicates what has given rise to failures. Sulfapyridine, sulphathiazole and sulfadiazine are all effective against the organism in vitro tests, but in order to be effective clinically they must be in high concentration at the site of the infection. As in postoperative endophthalmitis and panophthalmitis, early vigorous treatment is essential. The oral use of an ocularly absorbable sulfonamide compound, such as sulfadiazine, combined with the local application of an equally absorbable sulfonamide compound in the form of a powder, gives the best results. Iontophoresis is certainly of value in giving a rapid high concentration of these drugs in ocular tissue.

The editorial further states that:

. . . sodium sulphacetamide ('albucid') gives high levels in ocular tissues when introduced in fluid form into the conjunctival sac, but it is likely that under clinical conditions application in

ointment form is the better method. The values that have been reached with local application of sulphonamides are distinctly higher than those that can be safely reached by oral administration.

Sodium sulfacetimide is a soluble sulfonamide compound and, although not widely used in this country, will be used in the future because of certain advantages.

The editorial, in concluding, says that "it is clear that local therapy with soluble sulphonamides would be the method of choice." This statement should be emphasized in the light of recent clinical experience. As far as ophthalmology is concerned, the local use of the best sulfonamide compound in one of its available forms may entirely replace the more dangerous oral administration.

ALSON E. BRALEY, M.D., New York.

635 West One Hundred and Sixty-Fifth Street.

DESIGNATION OF VISUAL ACUITY

To the Editor:—Reference is made to the letter of Dr. Arthur Linksz appearing on page 662 of the April 1943 ARCHIVES. Attention is invited to the fact that this letter is in error as it pertains to "all tests given by the military services." The statement of Dr. Linksz is true with regard to the Navy and Coast Guard, whereas designation in the Army is in accordance with the standard Snellen procedure based on examining distance of 20 feet (6 meters).

Dr. Linksz's formula apparently would obtain for visual acuity designations up to 20/400 but is believed to require modification for poorer degrees of vision, such as 5/400.

EDWIN N. BEERY, Lieutenant Colonel, M.C., A.U.S.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

EPIDEMIC KERATOCONJUNCTIVITIS. M. SAUNDERS, F. D. GULLIVER, L. L. FORCHHEIMER and R. C. ALEXANDER, J. A. M. A. **121:** 250 (Jan. 23) 1943.

This article is based on the authors' clinical and experimental study of an outbreak in New York city. The following summary is given:

"1. Clinical, experimental and epidemiologic data have been obtained in 80 cases of epidemic keratoconjunctivitis.

"2. The following features were found to be diagnostically significant in all cases in this study: hyperemia and swelling of the palpebral conjunctiva, congested and hyperemic bulbar conjunctiva, edema of the lids and occasional pseudomembranes on the conjunctiva of the lower lid. In addition, lymph node involvement and the absence of discharge were found to predominate.

"3. Forty-two patients had corneal involvement. There has been no absorption of corneal opacities after a period of five months.

"4. Of the 42 cases of corneal involvement 14 (33⅓ per cent) showed impairment of vision varying from 5 to 15 per cent.

"5. The relationship between the ocular disease and systemic symptoms was investigated: 49 patients (61.2 per cent) complained of headaches, 9 patients having severe headaches; 26 patients (32.5 per cent) complained of malaise.

"6. In 3 cases severe systemic reactions occurred in the presence of a mild ocular disease. All patients with severe ocular involvement had systemic symptoms.

"7. Fifty-seven patients (71.2 per cent) lost from one to eight weeks from work because of epidemic keratoconjunctivitis.

"8. Epidemiologic data showed that there appeared to be individual predisposing factors present, but the nature of these factors is not fully understood. Of the 80 cases presented, 70 presented epidemic keratoconjunctivitis subsequent to ocular trauma or inflammation.

"9. In two of nine attempts, direct implantation of cultures with conjunctival scrapings yielded a filtrable virus which proved to be apparently identical with that isolated previously.

"10. The virus which was isolated on these two occasions produced definite symptoms in mice. It was neutralized by convalescent serum from a patient who had suffered from epidemic keratoconjunctivitis and who was not associated with the present group of patients.

"11. Nineteen convalescent serums from patients in this group were tested. Neutralizing antibodies against the virus varied from 100 to 10,000 mouse doses. The virus used in the neutralization experiments

was that isolated in an independent study of epidemic keratoconjunctivitis in New York city.

"12. In 6 of the 19 cases, antibody development was demonstrated. Specimens of serum taken as soon as possible after the onset of the disease were compared with specimens taken seventeen to thirty-four days after the first specimen was obtained. In all cases there was a distinct increase in the titers of the second samples, indicating a specific relationship between the virus and epidemic keratoconjunctivitis."

W. ZENTMAYER.

General Diseases

OCULAR FINDINGS IN CHILDHOOD ENDOCRINOPATHIES. C. APPLE and I. P. BRONSTEIN, Am. J. Ophth. **26:** 21 (Jan.) 1943.

Apple and Bronstein give the following summary and conclusions:

"The obesity (Fröhlich's?) patients are no different as to their ocular findings from any other normal group.

"The children who are of less-than-normal stature (pituitary origin), also do not vary as to their ocular findings from any other normal group. No evidence was found of visual disturbances from presumably altered secretions of the pituitary gland.

"The visual acuity of the hypothyroid patients, as a group, was below normal. Of these, 75 percent were hyperopic and 75 percent had more than 2 diopters of refractive error. Only one of the eight children was myopic.

"In the heterogenous group there were no pathologic ocular findings. The altered secretions causing the various abnormalities have apparently no effect upon the eye."

W. S. REESE.

VARICELLA AND THE CORNEA. H. D. ROSENBAUM, Am. J. Ophth. **26:** 53 (Jan.) 1943.

Rosenbaum remarks the paucity of ocular complications in chickenpox and reports the case of an officer in whom a central corneal ulcer developed as a late complication of this disease. It healed uneventfully, leaving a faint opacity, which permitted vision of 20/20 — 2. Rosenbaum feels that such complications may be more common than the literature suggests, since they are relatively mild and occur in children.

W. S. REESE.

Injuries

TRAUMATIC ULCER OF THE CORNEA WITH SPECIAL REFERENCE TO COAL MINERS. R. M. DICKSON, Brit. J. Ophth. **26:** 529 (Dec.) 1942.

Dickson gives the following summary:

"This report deals with a series of 437 traumatic ulcers of the cornea; 350 cases in the Royal Infirmary, Edinburgh, and 87 cases in the Glasgow Eye Infirmary.

"59.7 per cent occurred in coal miners.

"The bacteriology is shown in detail and includes the conjunctival flora of healthy miners. The pneumococcus was recovered from the

ulcer less frequently than was anticipated, but it was the commonest organism in the severe type of hypopyon ulcer. Dacryocystitis associated with hypopyon ulcer was present in 7.8 per cent of the Edinburgh cases, and was noted only once in the Glasgow series.

"The average stay in hospital was 16.2 days in Edinburgh, and 19 days in Glasgow.

"In 23.8 per cent of the total cases there was no useful vision left in the affected eye six months after discharge from hospital. Albucid Soluble [sodium sulfacetamide] eye drops in the first aid treatment of eye injuries in coal mines have been most successful in preventing infection and corneal ulcer."

W. ZENTMAYER.

Lids

GRANULOMA INGUINALE OF THE EYELID. A. L. WEINER, I. E. GAYNON and M. S. OSHERWITZ, Am. J. Ophth. **26:** 13 (Jan.) 1943.

Weiner, Gaynon and Osherwitz give the following summary and conclusions:

"1. A patient with an extragenital lesion of granuloma inguinale affecting the eyelid is described in detail.

"2. The diagnosis was established by the demonstration of Donovan bodies in the tissue of the eyelid, by the presence of clinical granuloma inguinale of the genitals, and by the response of specific therapy.

"3. The diagnostic hazards created by the presence of positive serologic tests for syphilis are reëmphasized."

W. S. REESE.

Orbit, Eyeball and Accessory Sinuses

PULSATING EXOPHTHALMOS: REVIEW OF ALL REPORTED CASES. J. D. MARTIN JR. and R. F. MABON, J. A. M. A. **121:** 330 (Jan. 30) 1943.

The authors report 5 cases of pulsating exophthalmos and supply the following summary and conclusion:

"There have been one hundred and sixty-three articles in major journals on pulsating exophthalmos since Locke's review in 1924; 224 additional cases have been reported through December 1941. Essentially all reports deal with the same problem previously discussed by Locke and others. It is noted that the choice of treatment is primarily operative. Ligation of the internal carotid was performed in 47 cases; of this number 25 were reported as cured. The common carotid was ligated in 43 instances with cures in 30. The ligation of multiple vessels, a combination of either the internal, external or common carotid and orbital veins, was carried out in 41 cases with twenty-seven cures. It is evident from such a summary that the results in all types of treatment are the same. The greatest contribution since 1924 has been, perhaps, the work of Dandy in ligating intracranially the carotid artery for the purpose of trapping the aneurysm. This procedure has been carried out six times, with 4 cases being reported as cured. It is advisable in many instances to undertake this operation when other methods fail.

"In this report a complete review of the literature since 1924 has been made. This brings the total reported cases to 812. Five additional operative cases are submitted by us. An explanation for the development of these conditions is made on the basis of anatomic studies of the cavernous sinus. This is the only example of a major artery within and a part of a large venous channel. Any trauma or disease to the artery would therefore allow an interchange of arterial and venous blood between these structures; thus an arteriovenous fistula would be formed. Basal fractures involving this area should be attended with the thought that a fistula may occur. In view of the progress of the disease, early treatment, namely ligation of the carotid artery, should be undertaken before extensive proptosis develops. This would decrease the danger of further destruction and blindness. Surgical treatment is beneficial, although many cases are followed by slight improvement and sometimes no change. There is no satisfactory direct operation to obliterate the fistula. This primarily is due to its location and association with vital structures."

W. ZENTMAYER.

Refraction and Accommodation

PRACTICAL IMPORTANCE OF ANISEIKONIA. E. JACKSON, Am. J. Ophth. **26:** 18 (Jan.) 1943.

Jackson discusses aniseikonia from the standpoint of refraction and reports 2 cases of monocular aphakia in which the patient learned to use both eyes with the correcting lenses. He concludes that if time is allowed for the establishment of new coordinations of vision, change in the size of images gives no trouble, and such coordinations are possible at all ages.

W. S. REESE.

ORIGIN OF MYOPIA. G. JANCKE, Klin. Monatsbl. f. Augenh. **106:** 264 (March) 1941.

Jancke reviews publications on the hereditary origin of myopia, discussing the theories of the most prominent authors in this field. His discussion centers on the question of whether or not close work increases myopia. The degree of myopia appears to be settled between the ages of 16 and 19. It is not known to increase during the fifth decade of life, although close work may be more intensive than in the second decade. The research is based on observation of 150 unselected pairs of twins. Tables illustrate the findings. Jancke's conclusions are as follows: The origin of myopia in close work has been denied by thorough researchers for many decades. Steiger's idea of the heredity of myopia has been supported by Jancke's observation on twins. Comparison of 8 monozygotic (identical) and 7 biovular pairs of myopic twins with equal schooling and similar professions has proved the decisive influence of heredity and has disproved the influence of close work. Consequently any recent theories to the contrary not supported by conclusive proof are untenable. Heredity cannot be denied as the predominant etiologic factor in myopia.

K. L. STOLL.

Retina and Optic Nerve

ARE WELDERS SUBJECT TO DEPLETION OF VISUAL PURPLE WHILE AT WORK? H. S. KUHN and E. C. WILLE JR., Am. J. Ophth. **26:** 69 (Jan.) 1943.

Kuhn and Wille give the following summary of their investigations:

"1. Sixty-one welders were given the Bio-photometer test for speed of dark adaptation before and after a day's work. Thirty-nine were on the day shift, 22 on the night shift.

"2. Half the welders (31) each received 10,000 units of vitamin A before starting work and again in the middle of the shift. The other welders received a placebo at the same time.

"3. There is no evidence of a general lack of dark adaptability among welders and no evidence of any decrement in this function during an eight-hour shift.

"4. Welders who received vitamin A showed no greater gain in dark adaptation than those who did not receive it. This should not be interpreted to mean that cases of vitamin-A deficiency would not respond to such treatment, nor that these welders would not respond with longer treatment or under different conditions.

"5. Individual differences in age, domicile, type of welding, goggles, and food showed no relation to differences in gain or loss of speed of dark adaptation during an eight-hour shift.

"6. Welders on the night shift showed a significant average gain in dark adaptation during their work. This is attributed to a greater demand for dark adaptation during periods when they were not actually welding. Several inferences are developed from this fact toward possible improvement of visual ease in welding by further visual engineering in this field.

"7. The clinical conclusion is that the excessive number of complaints among welders is due to inadequate protective equipment or carelessness in its use."

W. S. REESE.

CASE REPORT OF CONGENITAL GROUPED PIGMENTATION OF THE RETINA WITH MACULOCEREBRAL DEGENERATION. G. T. SCHWARZ, Am. J. Ophth. **26:** 73 (Jan.) 1943.

Schwarz reports the case of a 6 year old boy who was retarded in general intelligence and manual efficiency and who showed small flecks of pigment in the periphery of each retina similar to those seen in congenital grouped pigmentation. The maculas had a granular, dustlike, salt and pepper appearance with numerous pinpoint areas showing through. There were also high hyperopia and esotropia.

W. S. REESE.

ORIGIN OF OPTIC NEURITIS DURING LACTATION: REPORT OF CASES. K. WERNER, Klin. Monatsbl. f. Augenh. **106:** 314 (March) 1941.

Werner adds 2 cases of optic neuritis during lactation to the 3 cases reported by Glees. The women, aged 27 and 20, were primiparas.

The inflammation of the optic nerve began on the tenth and on the fifteenth day after delivery. Almost complete blindness disappeared entirely in the older patient after four weeks and in the younger after eight weeks. Each patient lost considerable blood during a difficult delivery. In the older woman purulent mastitis with a high fever and chills developed. The younger patient had erythema nodosum on one limb; she insisted on continuing to nurse her child after the onset of the optic neuritis. Werner agrees with Glees that infectious conditions are the cause of optic neuritis during lactation, which itself is only a weakening factor.

K. L. STOLL.

ETIOLOGIC VIEWPOINT IN SOME CASES OF UNDIAGNOSED OPTIC NEURITIS. W. EGGERT, Klin. Monatsbl. f. Augenh. **106:** 320 (March) 1941.

Eggert includes in the term optic neuritis such forms as papillitis, retrobulbar neuritis and peripheral interstitial neuritis, which are characterized by their localization in the optic nerve and which occasionally allow differential diagnostic conclusions relative to the causation. Genuine inflammatory conditions of the optic nerve are excluded, for instance, papilledema with hypertonic fundus and collateral edema with uveitis and optic perineuritis. The author reports 8 cases in which it was difficult to arrive at the cause. Exact neurologic and spinal fluid examinations, considered indispensable, were done in every case.

Multiple sclerosis predominated in cases of axial neuritis with or without papillitis. In the presence of neurologic symptoms which point to multiple sclerosis and disappear after a short rest cure, the diagnosis of multiple sclerosis appears certain, and it is probable even in the absence of neurologic symptoms, which often appear much later.

A toxic or direct inflammatory genesis of optic neuritis as a result of focal infection from sinuses, teeth or tonsils is acceptable only in cases in which neurologic examination gives normal results, recovery follows elimination of the focus and the neuritis is not influenced by an enforced rest cure. An ophthalmoscopic examination alone is insufficient for the diagnosis of either choked disk or papillitis; a neurologic examination, a test of the spinal fluid and a perimetric examination must be added. Tuberculous infection of the sheaths or septums of the optic nerve may be present in young patients with perineuritis or peripheral interstitial optic neuritis. Contraction of the field of vision, especially in the periphery, suggests a lesion of the peripheral portion of the optic nerve, and central scotomas, damage to the papillomacular bundles. Papillitis with a central scotoma is usually to be considered as a collateral edema caused by a lesion in the posterior central portion of the optic nerve.

Papillitis as a part of sympathetic inflammation is to be looked on as a transferred inflammation of the disk caused by choroiditis, even if it is not demonstrated by the ophthalmoscope, i. e., as a mild form of iridocyclitis. So-called sympathetic neuroretinitis, as a mild form of sympathetic ophthalmia, has a favorable prognosis.

K. L. STOLL.

Tumors

A Choroidal Melanoma Treated by Surgical Diathermy. L. H. Savin and G. C. Pritchard, Brit. J. Ophth. **26:** 551 (Dec.) 1942.

A man aged 37 complained of severe headache. In the course of the ocular examination a small melanoma of the choroid was discovered in the left eye. At the end of three weeks the growth was found to have increased in size. Because of the severe headaches metastasis was considered, and as visual acuity was 6/5 it was decided to destroy the growth by surgical diathermy. The ordinary 2.5 mm. flat electrode described by Weve was employed. The first application was about 1 disk diameter too far forward, but the second was right on the melanoma. Four months later the dead white diathermy marks were surrounded by pigment, but in the tumor area there appeared in the white ring a pigment patch which was less black and was the shape of the original tumor. This aroused the suspicion of a recurrence of the melanoma. Three months later the pigmentation was greater.

The patient cannot be considered out of danger. The "sighting shot" with the diathermy was made accidentally through faulty localization. A scar for comparison purposes on a normal area of retina proved, however, to be extremely valuable. The authors say, "We shall make such a scar deliberately in future cases, if by some fluke we strike the tumor at the first application."

The article is well illustrated.

W. Zentmayer.

Vision

Test Type. J. P. S. Walker, Brit. J. Ophth. **26:** 556 (Dec.) 1942.

Walker states that when a patient is placed 6 meters from the test type and is able to read what he ought to read at 4 meters or even 5, the obvious conclusion is that the test type is at fault and not that the patient has abnormally good sight. The author has taken twenty-five black and white squares arranged in the form of letters and placed them on a card of a neutral gray. This procedure gives twelve or thirteen white squares and a corresponding number of black, and no more, for the background is neither black nor white. With this arrangement only patients who truly have 6/6 vision can read the letters. It is immaterial whether the letters are formed with the white or the black squares. In practice it is better to have some in black and some in white. As far as possible the letters should be made up with twelve or thirteen squares. It is inaccurate when the patient cannot see 6/60 to bring him nearer the card. Letters to be seen at 90, 120, 150 and 180 meters should be employed at 6 meters.

The article is illustrated.

W. Zentmayer.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

DANIEL B. KIRBY, M.D., *Chairman*

R. TOWNLEY PATON, M.D., *Secretary*

February 15, 1943

Visual Functions. DR. SAMUEL T. ORTON (by invitation).

This paper will be published in full, with discussion, in a later issue of the ARCHIVES.

Chronic Orbital Myositis. DR. JOHN DUNNINGTON and DR. R. N. BERKE (by invitation).

This paper will be published in full, with discussion, in a later issue of the ARCHIVES.

Recession of the Inferior Oblique Muscle. DR. JAMES WATSON WHITE.

In an operation on the inferior oblique muscle alone, an incision is made through the conjunctiva 1 cm. to the outer side of the insertion of the external rectus muscle and just below this muscle. It is carried diagonally down and out at an angle of 15 degrees. Tenon's capsule is incised carefully, chiefly by blunt dissection, so that the inferior oblique muscle will not be cut by accident. When Tenon's capsule is engaged on a hook, a second hook is used and the dissection completed to the insertion. Sutures are taken in the muscle, and after the tenotomy the muscle is sutured to the sclera. The conjunctiva is closed by a running suture or interrupted sutures. The tenotomy is best done 2 to 3 mm. from the insertion. When complete paralysis is desired, no scleral sutures are taken.

In cases of paralysis of the inferior oblique muscle, a tuck is taken at this site. When one is combining recession of the inferior oblique with resection or recession of the external rectus muscle, the incision is that used in operations on the external rectus muscle. At the New York Post-Graduate Medical School and Hospital it is only rarely that any other method is used, and this method has been found to be more capable of modifications as to the effects than the others.

Operation on the inferior oblique muscle is indicated for the following purposes:

1. To correct a secondary deviation of the muscle due to paresis of the superior rectus muscle of the fellow eye.

2. To correct the secondary contraction due to paralysis of the superior oblique muscle of the same eye.

3. To shorten the inferior oblique muscle by tucking or other procedure in cases of paralysis of this muscle alone or in conjunction with paralysis of the superior rectus muscle of the same eye. This may be done by the method here described or at the origin, in the manner described by Wheeler in 1934.

4. To bring about complete paralysis of the inferior oblique muscle when this is desired in cases of either secondary deviation or secondary contracture. In such cases it makes little difference whether the tenotomy or myectomy is done at the origin or at the insertion. However, when resection is being performed on

the external rectus muscle to correct esotropia or recession to correct exotropia, in which operations it is a definite advantage to combine the procedures, as can readily be done.

The marked advantage of operating at the insertion is that the action of the inferior oblique muscle can be modified as the diagnosis requires, while in a tenotomy or myectomy at the origin no procedure so far devised has been satisfactory in limiting the effect with any degree of accuracy.

DISCUSSION

DR. JOHN H. DUNNINGTON: I have performed recession of the inferior oblique muscle during the past year about twelve times, and in no instance did it result in a complete paralysis of this muscle such as that which follows a simple tenotomy at the scleral insertion. Conservatism in the amount of recession has led to a few undercorrections. I should like to ask Dr. White whether he has ever repeated the operation when the first recession was insufficient.

The operation is easy to do when the external rectus muscle is reflected out of the way but rather difficult when that muscle is *in situ*. To my mind the most difficult part of the operation is proper alinement of the recession, i. e., making sure that the new attachment is in the normal line of pull of the muscle. I wonder whether Dr. White has any special technic that enables him to be certain of the correct position of the scleral suture.

The variability in the results obtained by myectomy of the inferior oblique muscle constitutes one of the strongest reasons for adoption of recession. One must not forget, however, that the scleral attachment of the inferior oblique muscle is close to the macula and that any undue traumatism may produce choroiditis sufficient to cause a paracentral scotoma.

The frequency with which the inferior oblique muscle is fused with the lower border of the external rectus is worthy of mention. Failure to recognize such fusion may lead to an unintentional severance of the oblique muscle at the time of resection of the external rectus muscle.

DR. LEE W. HUGHES (by invitation): It is my feeling that Dr. White has presented a reasonable approach to operation on the inferior oblique muscle. Recession of this muscle is a type of operation that ophthalmic surgeons are going to resort to more and more frequently as time goes on.

Most surgeons have had some spectacular results from tenotomy of the inferior oblique muscle as well as some disappointments. While tenotomies and myectomies have been done universally here and abroad, it has never seemed to be sound surgical procedure to cut a muscle and trust to luck as to just how much correction would follow.

It is my belief that there has not been sufficient time for evaluation of the results of the comparatively few recessions that have been performed but that, while definite conclusions cannot be drawn, the amount of lengthening which can be obtained by recession can be measured accurately.

Perhaps the day will soon arrive when some expert will be able to say just how much to recede an inferior oblique muscle in such and such a case. However, it is my feeling that there should be a careful measurement of the ocular deviations in all the cardinal directions of gaze as well as a thorough understanding of the case before any type of operation is performed.

Because of a suggestion by Dr. White, I did my first recession of an inferior oblique muscle May 7, 1940. When I was asked to discuss his paper, it was my thought that it might be well to make an analysis of the operations on muscles that had been performed in my service at the Newark Eye and Ear Infirmary since that date.

There were 148 patients who came for operation, and while approximately one half of these came from my private practice, the findings and results were practically the same in these as in the others.

In 69 (46 + per cent) either the elevator or the depressor group of muscles was involved, as follows: unilateral involvement of the superior rectus muscle, 37 patients; bilateral involvement of the superior rectus, 16; unilateral paralysis of the superior oblique, 5; unilateral paralysis of the inferior oblique, 4; bilateral paralysis of the inferior oblique, 1; spasm of the inferior oblique, 1; paralysis of the inferior rectus, 4; bilateral paralysis of the elevator muscles, 1.

Among the patients with unilateral convergent squint were the greatest number with unilateral paralysis of the superior rectus, while among those with alternating squint, whether convergent or divergent, were the greatest number with bilateral paralysis of the superior rectus muscle. Of the patients, 39 had monocular convergent squint, 28 alternating convergent squint, 7 monocular divergent squint and 2 alternating divergent squint, making 76 without vertical involvement.

During this period 22 recessions of the inferior oblique muscle, 3 of them bilateral, were done and 34 tenotomies of the inferior oblique, 3 of them bilateral.

I should like to show a few slides. The first presents a girl 8 years of age with a marked upshoot of the left eye, a rather large amount of convergent squint and amblyopia. There is a marked overaction of the left inferior oblique muscle with the eyes in right external rotation. A 3 mm. recession of the internal rectus and an 8 mm. resection of the left external rectus muscle, as well as a 5 mm. recession of the left inferior oblique muscle, were done. The next slide shows the final result, with the eyes straight in the primary position and no upshoot of the left eye with the eyes to the right.

The next slide shows a girl 9 years of age with paralysis of the right superior oblique muscle. An 8 mm. recession of the right inferior oblique muscle was done. The left hyperphoria present in the direction down and right before operation became right hyperphoria, while the right hyperphoria in the primary position became practically nil.

The next patient shown is a girl 11 years of age with double hyperphoria who had had a tenotomy on the right inferior oblique muscle but had considerable residual left hyperphoria. An 8 mm. recession of the left inferior oblique muscle was done. At the present time there is little hyperphoria in any of the cardinal directions of gaze.

The next patient is a girl 7 years of age with alternating convergent squint. Previous to her operation she appeared to have bilateral paralysis of the superior rectus muscle, but after bilateral resection of the external rectus muscle she showed 10 centrads of left hyperphoria. She had an 8 mm. myectomy of the right inferior oblique muscle at the origin, and at the present time there is only a trace of left hyperphoria. I present this slide merely to show that sometimes what appears to be bilateral hyperphoria previous to an operation later proves to be only unilateral hyperphoria and to show that myectomies do give good results.

Dr. Frank Conrad Keil: I have slides showing 2 patients whom Dr. White examined in consultation before operation. The first slides are of a patient for whom Dr. White advised a recession of 7 mm. for the right inferior oblique muscle and 5 mm. for the left, instead of 9 mm. and 7 mm., as he stated in his paper. The patient was 4½ years of age. She had 0.5 D. of myopia. Although the error was slightly undercorrected, she had binocular fixation.

The other child was 6 years of age. She had hypermetropia of 8 D., esotropia of 40 degrees for distant and 60 degrees for near vision and hyperphoria of over 25 degrees when looking up and in. The hyperphoria could not be measured accurately. The right inferior oblique muscle was receded 9 mm. and the left 7 mm. The results of operation were excellent.

Dr. Conrad Berens: Because there now exist records of 57 recessions of the inferior oblique muscle performed at the New York Eye and Ear Infirmary, I thought a word should be said as to the results, since in my judgment Dr. White has made an outstanding contribution to the surgical correction of vertical imbalance and especially to surgical procedures on the inferior oblique muscle. This opera-

tion can be graduated better than a myotomy or myectomy. There are one or two points which help the surgeon to be more accurate in his work. One is scleral fixation with a bipronged scleral hook, which permits exposure of the insertion of the inferior oblique muscle and the sclera where the suture is inserted, and the other is grasping of the muscle at its insertion with a special forceps. I have been inserting a double-armed nylon suture (Davis and Geck) because I have less reaction with this material than with any other. Dr. Peter at the American Ophthalmological Society meeting in 1942 said that one should not perform this operation unless one also detaches the lateral rectus muscle, but I did not do this in operating on 9 private patients and believe it is unnecessary. I do not agree that one should tenotomize at a distance from the insertion of the muscle because it lies over the macular region. Although I was afraid at first of detaching the muscle at its insertion, I am so no longer, particularly if Stevens' scissors with the points upward are used and an illuminated retractor employed. The results obtained by these means have been excellent, and no complications have developed, in 18 operations I performed myself and in 7 other operations performed in my service. I was able to judge accurately the results of 9 operations which I performed without touching the other muscles. Slight overcorrection occurred in 2 cases, but in the majority there was undercorrection. In 1 case myectomy had to be performed after recession. The undercorrection probably resulted from the small recessions performed at first, 3 and 4 mm. and later 5 and 7 mm. More recently, especially after hearing Dr. White's discussion at the American Ophthalmological Society, I have receded the muscle 9 or 10 mm. I have found that in very small children when the muscle is being receded 9 mm. if one branch of the caliper is placed underneath the scleral insertion of the inferior oblique muscle the other branch overlies the inferior temporal vortex vein.

The results on the whole have been excellent. The following procedures were used in the operations on the 35 clinic patients; recession of the inferior oblique combined with resection of the lateral rectus muscle, 17 patients; recession of the inferior oblique combined with recession of the medial rectus muscle, 9 patients; a combination of recession and resection, 2 patients; isolated recession of the inferior oblique muscle (unilateral), 4 patients, and isolated double recession of the inferior oblique muscle, 3 patients. The average amount of recession was 6.5 mm., the greatest 10.0 mm. and the smallest 3.0 mm.

It is early to give accurate figures on the amount of recession required, but 20 prism diopters of vertical imbalance in the field of the inferior oblique muscle requires approximately 8 mm. of recession. A patient with this amount of deviation in the field of the inferior oblique muscle would probably show from 5 to 8 prism diopters of vertical imbalance in the primary position with the screen test and prisms. This of course would depend on fixation.

The functional results obtained in 34 clinic patients are as follows: heterophoria or orthophoria in the primary position, 29 patients, and slight remaining heterotropia, 5 patients. One patient was not observed after operation.

I cannot speak of the results in the private patients, because the entire series of 57 operations has not been thoroughly analyzed, but it has been proved that Dr. White has made a splendid contribution.

DR. JAMES W. WHITE: I thank the discussers for their remarks. Dr. Dunnington spoke of complete paralysis of the inferior oblique muscle such as that which follows a simple tenotomy at the scleral insertion. I do not tenotomize at the scleral insertion but withdraw 2 mm. before severing the muscle. Some operators have used the muscle hook to grasp it instead of putting in a suture. I prefer the suture. I wish I had had Dr. Dunnington's experience of never having had complete paralysis when tenotomy was done at the origin.

Dr. Keil was too modest to speak of his method of performing the recession operation. He took a double arm suture through the sclera, underneath the muscle and through the muscle just short of the insertion. After tenotomy, the suture

was tied and the muscle reattached to the sclera. This is a good method if one feels any uncertainty about keeping the line of traction of the muscle, and I would recommend that others try it. I congratulate Dr. Keil on his technic.

Dr. Hughes brought up one point I wish to emphasize, and that is the exactness of the diagnosis. One has to know whether a tenotomy of the oblique muscle is indicated. One has to know the deviations, measured not only in the primary position but in the cardinal positions before a diagnosis can be made.

In regard to Dr. Berens' discussion, I have never happened to contact the vortex vein. I have done all my tenotomies on the inferior oblique muscle at the insertion, feeling that the more I did there, the better judgment I should have in the cases to come. The only time I use another approach to the muscle is when teaching the house surgeons, when occasionally I tenotomize the inferior oblique muscle through a cutaneous incision.

Epidemic Keratoconjunctivitis: Isolation and Identification of a Filtrable Virus. DR. MURRAY SANDERS.

This article was published in part in the October 1942 issue of the ARCHIVES, page 581, and in the January 1943 issue of the *Journal of Experimental Medicine*, page, 71.

Epidemic keratoconjunctivitis, which has made its appearance in continental United States within the past two years, was discussed from clinical and research aspects.

The disease is a distinct clinical entity and may be diagnosed on the basis of the following criteria: acute follicular conjunctivitis with scanty exudate, regional enlargement and tenderness of lymph nodes, negative results of bacteriologic examinations, mononuclear cellular exudate and punctate keratitis with lesions of varying size. The corneal involvement, found in 30 to 80 per cent of the cases, occurs one week to ten days after the onset of the disease.

A series of cases were studied experimentally in an effort to determine the hitherto unknown etiologic agent. A virus was isolated in 2 by passage of conjunctival scrapings or emulsion of infected mouse brains into tissue cultures. The tissue culture passage resulted in intensification of symptoms, stabilization of the incubation period and production of two stable strains of virus. Previous to the isolation, mice inoculated intracerebrally with human conjunctival scrapings or infected mouse brain emulsion showed only vague symptoms, which developed within varying periods and were transmissible for only a few mouse passages. After isolation of the virus the course of the disease in mice became well defined and the incubation period clearcut.

DISCUSSION

DR. ALSON E. BRALEY: Dr. Sanders is to be congratulated for a beautiful piece of research. The ingenious technic for the isolation of the virus required considerable thought. The disease entity in itself is not easily diagnosed, at least in the early stages.

I will limit my remarks to three points: (1) the differential diagnosis, (2) the question of whether there is actually an epidemic on the East Coast and (3) treatment.

As to differential diagnosis, the two main diseases that are most difficult to distinguish are Béal's conjunctivitis and inclusion conjunctivitis. I should like to show a series of kodachrome pictures of epidemic keratoconjunctivitis. [Slides were shown.] As may be seen, a few petechial hemorrhages may be present on the surface, but the most striking findings are the severe discomfort and the amount of bulbar chemosis. Occasionally a pseudomembrane will form on either the upper or the lower lid, and there may be a great many hemorrhages on the bulbar conjunctiva, both conditions being associated with edema. The corneal changes are typical, appear chiefly in the central pupillary area and may occur bilaterally.

The first disease to be considered in the differential diagnosis is inclusion conjunctivitis, which frequently gives rise to enlargement of the preauricular lymph nodes and severe follicular conjunctivitis. In this disease there is not as much discomfort or as much edema of the bulbar conjunctiva, but the follicular hyperplasia is more pronounced. However, as can be seen from the kodachrome pictures, inclusion conjunctivitis may be identical in appearaance with epidemic keratoconjunctivitis. The finding of inclusion bodies is then of diagnostic value.

The second disease to consider in the differential diagnosis is Béal's conjunctivitis. In this disease one sees edema and enlargement of the preauricular lymph nodes, but little discharge. The discharge is the type of exudate that occurs in Béal's conjunctivitis, which is the same as that in keratoconjunctivitis. The differential diagnosis is not easy, and, consequently, on the West Coast a number of ophthalmologists have said that Béal's conjunctivitis represents a mild form of keratoconjunctivitis or that keratoconjunctivitis represents a more severe form of Béal's conjunctivitis. If that were true one would expect neutralizing antibodies in the latter disease. A number of patients with Béal's conjunctivitis whom Dr. Sanders studied have been tested and do not have neutralizing antibodies.

The next point is whether there is at present an epidemic. Close to 600 cases have been noted in New York and its outlying districts. I personally have observed, or have had something to do with, 209 cases in New York. Approximately 500 cases have been noted in Schenectady, N. Y., and on the basis of the survey conducted by the New York State Department of Health it was figured that there were 1,600 cases there. On the basis of the number of cases encountered in New York, approximately 200, there should be about 600 cases there.

Finally, concerning treatment, that used has not been of much value and little has been said about treatment because there have been no specific therapeutic agents. Almost everything that has been used makes the patient worse, including sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) ointment. I realize it was reported in *The Journal of the American Medical Association* that treatment with sulfathiazole solution made a number of patients better, but I have not found this of value. An anesthetic is of some value, especially to make the patient more comfortable. I have treated 12 patients with intravenous injections of convalescent plasma and serum, knowing it contains neutralizing antibodies for the virus. The amount of plasma used has varied between 15 and 75 cc. Patients with the more severe form seem to require a good deal of the plasma. Those who received in the neighborhood of 50 cc. seemed to do the best. Of the 12 who have been treated, the result in only 1 has been a failure, and I believe that if this patient could have been followed more closely he might have been given more plasma. The history is essentially as follows: Convalescent plasma or serum is given intravenously, and within twenty-four hours the patient has complete symptomatic relief. Within forty-eight hours he is almost clinically cured. He still has a moderate amount of conjunctival infiltration. However, within seventy-two hours to four days he is much improved. Of the series under discussion, severe corneal changes have developed in only 1 patient.

Book Reviews

Neurologia Ocular. By Esteban Androgué. Pp. 889, with 506 illustrations. Buenos Aires, Argentina, El Ateneo, 1942.

This excellent book testifies to the advance of modern medicine in Argentina and to the high scientific level of the men and institutions of that country. It represents a great amount of work and clinical experience. Its author has studied the literature of ocular neurology in a thorough and comprehensive way.

An introduction is devoted to the bioelectric phenomena which take place in the nervous system. The subject matter is divided into four parts: (1) ocular effector system, (2) ocular receptor system, (3) hereditary diseases in relation to ophthalmology and (4) complementary subjects.

In the first part the oculomotor apparatus of the eye is considered from the anatomic and phylogenetic points of view. The physiology of ocular movements is studied in a special chapter. Then come the vestibular functions, binocular movements, heterophorias, insufficiency of convergence, strabismus both concomitant and paralytic, ophthalmoplegias, congenital anomalies, spastic crisis, nystagmus, etc. In discussing the effector autonomic system, the author describes the sympathetic and parasympathetic action, the motility and pathologic disturbances of the iris, accommodation and its disturbances and ocular sympathetic syndromes.

In the second part he deals with the sensorial apparatus of the eye. After an anatomic discussion he describes neuroparalytic keratitis, corneal herpes, herpes zoster and ocular neuralgias. A special chapter deals with the phylogenesis, anatomy and physiology of the retina. Then come the ophthalmoscope, the functional examination of vision and disturbances in the perception of form, light and color.

Diseases of the optic nerve are presented in a complete manner. The discussion on papilledema is illuminating and contains original data from the author's clinical experience.

Balado's original study of intracranial hypertension due to chronic edema of the brain is fully described. The chapter on atrophies of the optic nerve is well written and illustrated.

Another personal contribution of Androgué is the thorough discussion of chiasmatic syndromes, with a description of interesting clinical cases. It is excellently illustrated with pictures, charts, schemata and roentgenograms. Chapter XV deals with diseases of the external geniculate body, optical radiation and calcarine fissure. Hemianopsia, cortical blindness, and optical gnosia and agnosia are discussed in detail.

The third part of the book deals with hereditary ophthalmic diseases and presents the subject in a complete and practical way. The study of the tumors and pseudotumors of the retina, of hemangiomas, of Hippel's disease, etc., is well done. Lipoidosis in ophthalmology takes a whole chapter.

The fourth and last part of the book deals with diseases of the retinal vessels, disturbances of the circulation in the retina and ocular syphilis. The book ends with a study of vitamins, their influence in visual disturbances and an enumeration of allergic conditions.

All the subjects are well presented and discussed, especially those which refer to neurologic diseases. The illustrations are all good, but the lack of color plates for fundus lesions is to be regretted.

The reviewer thinks that an English translation should be made, so that this excellent contribution to ophthalmology would be accessible to all English-speaking physicians.

MANUEL URIBE TRONCOSO.

The Vertebrate Eye and Its Adaptive Radiation. By Gordon Lynn Walls, Sc.D. Price, $6.50. Pp. 785, with 197 illustrations. Bloomfield Hills, Mich.: Cranbrook Institute of Science, 1942.

Dr. Walls has written a comprehensive treatise on the vertebrate eye in which he includes and correlates an immense amount of data on the anatomy and physiology of the eye in relation to the various environments in which it functions. The 689 pages of text are very readable, appealing to the interests of the biologist, clinician or lay reader, and constitute, therefore, as the author intended, rather a textbook on the eye than merely a reference source.

There are three major divisions of the text. The first, entitled "Basic," consists of a discussion of the anatomy and histology of the human eye and orbit. Adequate material on the structure of the retina is followed by a clear and welcome discussion of the theories of the visual processes, including color vision. In addition there is a brief résumé of the development of the eye.

The second division concerns itself with ocular adaptations which may be correlated with the living habits of the species. Such subjects as night and day vision and the adaptation of the eye to aqueous and gaseous mediums are of particular appeal to the student of biology. The peculiar modifications of the eye of some of those animals which require air and water vision is the subject of an intensely interesting section. The physiologic mechanisms invoked in various vertebrates to achieve accommodation, aid in depth and movement perception and accomplish protective coloration are described and discussed in detail.

The third section, called "Synoptic," consists of an excellent study of the comparative anatomy of the vertebrate eye. Examples are thoroughly described and illustrated. The contributions of such studies of ocular anatomy to the knowledge of vertebrate phylogeny are emphasized.

This textbook will certainly be welcomed by ophthalmologists as well as biologists. It is clearly written, if somewhat given to modern colloquialism. There has been gathered within it and organized much of the present knowledge of the physiology and anatomy of human and animal eyes, heretofore scattered in many technical papers and languages.

The book closes with a twenty-four page bibliography and an index which includes a glossary. The glossary is a valuable addition. While it is stated that the bibliography represents "but a tiny portion of the whole literature of the eye," it seems that the recent work of several laboratories might have been included with advantage. An unusual feature, which concludes the bibliography, consists of a list of scientists who, in the author's opinion, "are likely to be especially productive" or are "prolific" and not "wholly trustworthy." Such lists probably exist in the minds of most workers but are rarely published.

GEORGE K. SMELSER.

Oftalmoscopia Clinica. By Tomas R. Yanes. Price, $6.00. Pp. 500 with illustrations in black and in color. Habana: Biblioteca médica de Autores Cubanos, 1943.

The author is well known in this country as a representative of progressive Cuban ophthalmology. The publication of this book is part of the movement which has spread to many countries in Latin America to have their own medical literature, written in Spanish, by their own authors, and not to be dependent on textbooks in other languages (especially those written in French) or on translations of English and German works made in Spain and usually not very up to date.

The publication of medical books in Latin America, with the probable exception of Argentina, is a difficult and costly enterprise and rarely a financial success. It is probable that Dr. Yanez had some difficulties in printing and especially in illustrating his book. For color pictures he had to use reproductions of Oeller's "Atlas of Fundus Diseases." Unfortunately the black and white illustrations are mainly photographs which do not show up well. Some of them are blurred and

lacking in detail, failing to give the reader an accurate idea of the conditions represented. Since ophthalmoscopy is especially a visual activity on the part of the observer, who tries to store visual images to use later in observation and diagnosis, a textbook should have a background of precise and faithful color representations of fundus diseases. Perhaps in later editions Dr. Yanez may be able to correct the defective pictures, thus enhancing the value of his work. The book is primarily intended for students and medical practitioners. It is the outgrowth of a course given by the author at the Eighth National Medical Congress of Cuba, and its purpose is to encourage a more widespread use of the ophthalmoscope. The fundus in the normal eye is discussed briefly. The descriptions of fundus diseases are short and written from the clinical standpoint. Rarely is a pathologic basis sought for the explanation of changes in the inner membranes. Some diseases are only mentioned, for instance, diffuse choroiditis.

The author—undoubtedly to be thorough—has added at the end material on such matters as fundus lesions in focal infections. In another chapter he deals with diseases of the female genitals, in association with which he describes retinitis of pregnancy, included by other authors in the chapter on renal retinosis. An interesting chapter is devoted to prognosis from the standpoint of fundus lesions.

The book is timely, and it is hoped that it will bring the subject of ophthalmoscopy to the attention of general physicians in Cuba and encourage a widespread use of the instrument.

MANUEL URIBE TRONCOSO.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Rua Consolacão, São Paulo, Brazil.
Place: Montevideo, Uruguay. Time: Nov. 4-9, 1943.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chinese Ophthalmology Society

President: Dr. C. H. Chou. 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. I. Iwre, Budapest.
Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Mária-utca 39, Budapest.
All corespondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Secretary: Mr. L. H. Savin, 7 Queen St., London, W. 1, England.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time First Friday of every month.

OXFORD OPHTHALMOLOGICAL CONGRESS

Master: Mr. P. G. Doyne, 60 Queen Anne St., London, W. 1, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.
Place: Oxford, England. Time: July 8-9, 1943.

PALESTINE OPHTHALMOLOGICAL SOCIETY

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

POLISH OPHTHALMOLOGICAL SOCIETY

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President: Col. F. A. Juler, 96 Harley St., London, W. 1, England.
Secretary: Dr. Harold Ridley, 60 Queen Anne St., London, W. 1, England.

SÃO PAULO SOCIETY OF OPHTHALMOLOGY

President: Dr. W. Belfort Mattos, Caixa Postal, 4086, São Paulo, Brazil.
Secretary: Dr. Silvio de Almeida Toledo, Enfermaria Santa Luzia, Santa Casa de Misericordia, Cesario Motta, St. 112, São Paulo, Brazil.

SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November, inclusive.
All correspondence should be addressed to the President.

SOCIEDADE DE OPHTHALMOLOGIA E OTO RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Theonilo Amorim, Barra Avenida, Bahia, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

Société Française d'Ophthalmologie

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

Society of Swedish Ophthalmologists

President: Prof. K. G. Ploman, Stockholm.
Secretary: Dr. K. O. Granström, Södermalmstorg 4 Ill tr., Stockholm, Sö.

Tel Aviv Ophthalmological Society

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

American Medical Association, Scientific Assembly, Section on Ophthalmology

Chairman: Dr. Conrad Berens, 35 E. 70th St., New York City.
Secretary: Dr. Derrick Vail, 441 Vine St., Cincinnati.

American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology

President: Dr. Ralph I. Lloyd, 14–8th Ave., Brooklyn.
President-Elect: Dr. James A. Babbitt, 1912 Spruce St., Philadelphia.
Executive Secretary-Treasurer: Dr. William L. Benedict, 101—1st Ave. Bldg., Rochester, Minn.

American Ophthalmological Society

President: Dr. Hunter H. McGuire, 105 N. Braddock St., Winchester, Va.
Secretary-Treasurer: Dr. Walter S. Atkinson, 129 Clinton St., Watertown, N. Y.
Place: Hot Springs, Va. Time: May 31-June 2, 1943.

Association for Research in Ophthalmology, Inc.

Chairman: Dr. John Evans, 23 Schermerhorn St., Brooklyn.
Secretary-Treasurer: Dr. C. S. O'Brien, University Hospital, Iowa City.

Canadian Medical Association, Section on Ophthalmology

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

Canadian Ophthalmological Society

President: Dr. Colin A. Campbell, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. Kenneth B. Johnston, Suite 1, 1509 Sherbrooke St., W., Montreal.

National Society for the Prevention of Blindness

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

Academy of Medicine of Northern New Jersey, Section on Eye, Ear, Nose and Throat

President: Dr. Charles W. Barkhorn, 223 Roseville Ave., Newark.
Secretary: Dr. William F. McKim, 317 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

Central Wisconsin Society of Ophthalmology and Otolaryngology

President: Dr. D. G. Hugo, 130 Main St., Oshkosh.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

New England Ophthalmological Society

President: Dr. Harry C. Messinger, 210 Angell St., Providence, R. I.
Secretary-Treasurer: Dr. Merrill J. King, 82 Commonwealth Ave., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, Time: 8 p. m. third Tuesday of each month from November to April, inclusive.

Pacific Coast Oto-Ophthalmological Society

President: Dr. Ralph A. Fenton, 1020 S. W. Taylor St., Portland, Ore.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

Puget Sound Academy of Ophthalmology and Oto-Laryngology

President: Dr. L. L. McCoy, 1317 Marion St., Seattle, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 301 Stimson Bldg., Seattle.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month except June, July and August.

Rock River Valley Eye, Ear, Nose and Throat Society

President: Dr. J. Sheldon Clark, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

Saginaw Valley Academy of Ophthalmology and Otolaryngology

President: Dr. M. Kessler, 311 Center Ave., Bay City, Mich.
Secretary-Treasurer: Dr. J. H. Curts, 330 S. Washington Ave., Saginaw, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

Sioux Valley Eye and Ear Academy

President: Dr. J. C. Davis, 1615 Howard St., Omaha.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux Falls, S. D.

Southern Medical Association, Section on Eye, Ear, Nose and Throat

Chairman: Dr. L. Chester McHenry, Medical Arts Bldg., Oklahoma City.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.
Place: Richmond, Va. Time: November 1942.

Southwestern Academy of Eye, Ear, Nose and Throat

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.
Place: Albuquerque, N. Mex. Time: November 1942.

Southwestern Michigan Triological Society

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

Western Pennsylvania Eye, Ear, Nose and Throat Society

President: Dr. C. H. Bailey, 29 S. Oakland Ave., Sharon.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

Arkansas State Medical Society, Eye, Ear, Nose and Throat Section

President: Dr. R. R. Kirkpatrick, 6th and Walnut Sts., Texarkana, Ark.
Secretary-Treasurer: Dr. Raymond C. Cook, 701 Main St., Little Rock.

Colorado Ophthalmological Society

President: Dr. William M. Bane, 1612 Tremont Pl., Denver.
Secretary: Dr. Harry Shankel, Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

Connecticut State Medical Society, Section on Eye, Ear, Nose and Throat

President: Dr. Edward N. DeWitt, 836 Myrtle Ave., Bridgeport.
Secretary-Treasurer: Dr. Henry L. Birge, 179 Allyn St., Hartford.

Eye, Ear, Nose and Throat Club of Georgia

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer: Dr. C. K. McLaughlin, 567 Walnut St., Macon.

Indiana Academy of Ophthalmology and Oto-Laryngology

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

Iowa Academy of Ophthalmology and Oto-Laryngology

President: Dr. J. K. Von Lackum, 117-3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

Lousiana-Mississippi Ophthalmological and Otolaryngological Society

President: Dr. Henry N. Blum, 912 American Bank Bldg., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

Michigan State Medical Society, Section of Ophthalmology and Otolaryngology

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmology and Otolaryngology

President: Dr. Erling Wilhelm Hansen, 78 S. 9th St., Minneapolis.
Secretary-Treasurer: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. William J. Marshall, 335 Owen St., Missoula.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr. Edgar P. Cardwell, 47 Central Ave., Newark.
Secretary: Dr. Arthur E. Sherman, 243 S. Harrison St., East Orange.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. M. R. Gibson, Professional Bldg., Raleigh.
Secretary: Dr. Vanderbilt F. Couch, 105 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. T. W. Buckingham, 405 Broadway, Bismarck.
Secretary-Treasurer: Dr. F. L. Wicks, 516-6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Bailey, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. R. S. Fixott, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. E. L. Goar, 1300 Walker Ave., Houston.
Secretary: Dr. Dan Brannin, 929 Medical Arts Bldg., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Everett B. Muir, Boston Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 623 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. Ferguson, Second National Bldg., Akron, Ohio.
Secretary-Treasurer: Dr. D. F. Mathias, First Central Tower, Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Stacy C. Howell, 144 Ponce de Leon Ave. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., second Wednesday of each month, from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. William B. Agan, 1 Nevins St., Brooklyn.
Secretary-Treasurer: Dr. Benjamin C. Rosenthal, 140 New York Ave., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Meyer H. Riwchun, 367 Linwood Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Sanford Gifford, 720 N. Michigan Ave., Chicago.
Secretary-Treasurer: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. W. J. Abbott, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. L. V. Johnson, 2065 Adelbert Rd., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Francis H. Adler, 313 S. 17th St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. William A. Stoutenborough, 21 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. D. G. Sanor, 206 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. F. K. Stroud, 416 Chaparral St., Corpus Christi, Texas.
Secretary: Dr. Arthur Padilla, 414 Medical Professional Bldg., Corpus christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. S. F. Harrington, 921 Medical Arts Bldg., Dallas, Texas.
Secretary: Dr. Abell Hardin, Medical Arts Bldg., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Dr. Howell L. Begle, 2730 E. Jefferson Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Time: 6:30 p. m., first Wednesday of each month.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. James M. Dunn, 1352 Union St., Schenectady.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Eastern Pennsylvania Association of Eye, Ear, Nose and Throat Physicians

President: Dr. James E. Landis, 232 N. 6th St., Reading.
Secretary-Treasurer: Dr. Sterling F. Mengel, 612 W. Market St., Pottsville.
Time: Last week in April each year.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. W. R. Thompson, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. A. E. Jackson, 602 W. 10th St., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Felician J. Slataper, 1110-1111 Medical Arts Bldg., Houston, Texas.
Secretary: Dr. Theo. L. Holland, 611 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. John I. Garret, 57 Stokes Bldg., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Homer Beal, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. Desmond Curran, Federal Reserve Bank Bldg., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.
Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. Sylvester H. Welch, 102 N. Brand Blvd., Glendale, Calif.
Secretary-Treasurer: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. E. J. Cummings, 1835 I St. N. W., Washington.
Secretary: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. John W. Truitt, 161 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. Andrew Hollabaugh, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Guy Maness, Medical Arts Bldg., Nashville, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.
Secretary: Dr. Frederick A. Wiess, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Otolaryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. Daniel B. Kirby, 780 Park Ave., New York.
Secretary: Dr. R. Townley Paton, 927 Park Ave., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. Isidore Givner, 108 E. 66th St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. R. E. Leatherock, Cushing, Okla.
Secretary: Dr. Harry C. Ford, 1014 Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Leo P. Coakley, 918 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m., program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. L. Markowitz, 16 Church St., Paterson, N. J.
Secretary-Treasurer: Dr. A. John Reinhorn, 302 Broadway, Paterson, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

President: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Secretary: Dr. Glen Gregory Gibson, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLGICAL SOCIETY

President: Dr. Hunter H. Turner, 717 Liberty Ave., Pittsburgh.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Solon L. Rhode, 238 N. 6th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

RICHMOND OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. F. Bryce, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. Richard W. Vaughan, Medical Arts Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. E. J. Avery, 11 N. Goodman St., Rochester N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester. N. Y.

St. Louis Ophthalmic Society

President: Dr. Leslie C. Drews, 508 N. Grand Blvd., St. Louis.
Secretary: Dr. H. Rommel Hildreth, 823 Metropolitan Bldg., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting, 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Dan Russell, 705 E. Houston St., San Antonio, Texas.
Secretary-Treasurer: Dr. P. G. Bowen, 315 Camden St., San Antonio, Texas,
Place: Bexar County Medical Library. Time: 8 p. m., first Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Fred Boyle, 490 Post St., San Francisco.
Secretary: Dr. Frank Hand, 450 Sutter St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Andrew de Roetth, 422 W. Riverside Ave., Spokane, Wash.
Secretary: Dr. Paul A. Remington, 422 W. Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. Roy Seeley Moore, 1704 State Tower Bldg., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. John D. Skow, 2001 Collingwood Blvd., Toledo, Ohio.
Secretary: Dr. S. H. Patterson, 125–15th Ave., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. L. Conner Moss, 3260 Wilson Blvd., Arlington, Va.
Secretary-Treasurer: Dr. Harold R. Downey, 1740 M St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.

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